University of Alberta

A Systematic Review of the Effectiveness of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Associated With Chronic Obstructive Pulmonary Disease and Restrictive Pulmonary Disorders

by

Mary Ann Bernadette Kolodziej ©

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Dedication

This project is dedicated to my wonderful family; husband Richard, daughter Genevieve, and sons Nicolas and Stanley, who have been very patient and understanding, and a great source of support during the time I dedicated to completion of this thesis.

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Chapter One

Introduction

Chronic respiratory failure (CRF) due to chronic obstructive pulmonary disease (COPD) and restrictive pulmonary disorders contribute a significant social and economic burden to individuals, families, and the health care system. The incidence of COPD alone, in terms of combined mortality and disability, was twelfth highest worldwide in 1990 and is expected to become fifth highest worldwide by 2020, with mortality expected to increase fivefold by 2015 (Ait-Kaled, Enarson, & Bousquet, 2001; Anto, Vermiere, Vesto, & Sunyer, 2001; Murray & Lopez, 1996). COPD as well as many restrictive pulmonary disorders (including myopathic disorders, muscular dystrophies, myasthenia gravis, amyotrophic lateral sclerosis, multiple sclerosis, postpolio syndrome, and thoracic wall deformities due to kyphoscoliosis or previous thoracoplasty), are indolent and progressive, and result in gradually increasing ventilatory impairment. Escalating health care costs associated with increasing disability and morbidity occur with disease progression and the development of worsening chronic respiratory failure (CRF) in both COPD and restrictive pulmonary disorders.

Although the mechanisms underlying alveolar hypoventilation in chronic respiratory failure associated with COPD and restrictive pulmonary disorders may differ somewhat, the resulting degrees of nocturnal and daytime abnormality in gas exchange, sleep disordered breathing, dyspnea, and increased work of breathing, contribute to significant functional impairment, morbidity, and mortality (American Thoracic Society, 1995). Within the last few decades, varying options for different forms of noninvasive positive pressure mechanical ventilation (NIPPV) to manage chronic respiratory failure have been developed, including bilevel positive airway pressure. While bilevel NIPPV has been introduced as a temporizing measure to manage the daytime symptoms of hypoventilation associated with chronic respiratory failure due to restrictive pulmonary disorders, conflicting study results have precluded it's use in stable chronic respiratory failure due to COPD (Criner, Brennan, Travaline, & Kriemer, 1999; Mehta & Hill, 2001).

Background

Chronic Obstructive Pulmonary Disease (COPD)

COPD is characterized by persistent airflow obstruction. The rate of progression, the extent of airflow obstruction and airway hyperreactivity, as well as impairment in alveolar ventilation and gas exchange, contribute to the heterogeneity of COPD and the extent of chronic bronchitic versus emphysematous change that occurs. Purely chronic bronchitic patients typically have a total lung capacity (TLC) which is relatively normal, slightly increased residual volume (RV), some inspiratory and expiratory airflow obstruction, normal elastic lung recoil and compliance, and normal carbon monoxide alveolar diffusing capacity, whereas purely emphysematous patients most often have increased RV:TLC ratio, increased TLC, expiratory airflow obstruction with preserved inspiratory flow, reduced elastic lung recoil, and increased lung compliance (Reis, 2001). Both chronic bronchitis and emphysema have associated derangements in gas exchange with disease progression, however parenchymal changes in emphysema resulting from hyperinflation and alveolar hyperinflation and capillary destruction contribute to reduced diffusing capacity, as well as hypoxemia and hypercapnia that are increasingly refractory to current conventional COPD therapeutic modalities. The combination of parenchymal and mechanical changes associated with severe COPD, including airway obstruction, alveolar air-trapping, reduced alveolar diffusing capacity, and dynamic hyperinflation, contribute not only to ventilation-perfusion mismatch and derangements in gas exchange, but also create a heightened elastic and resistive load on the respiratory muscles (Begin, 2000; Elliott, 1995; Reis, 2001). Increased work of breathing and heightened inspiratory effort is required to sufficiently overcome the mechanical load (elastase and resistance) in an attempt to normalize alveolar ventilation (Breslin, 1996; Elliott, 1995). Consequently, patients with severe stable COPD function at the upper limit of capacity in an effort to sustain adequate alveolar ventilation and gas exchange (Begin, 2000; Clark & Wilcox, 1997). Increased carbon dioxide (CO2) output from heightened respiratory muscle work of breathing, as well as lactic acid production, contribute to declining inspiratory muscle strength and endurance, and predispose patients with severe chronic COPD to respiratory muscle fatigue and recurrent episodes of COPD exacerbation (Begin, 2000; Nishimura, Izuma, Tsukino, & Oga, 2002).

Treatment strategies for COPD have largely focused on optimizing lung function, management of symptoms and disease-associated debilitating systemic effects (respiratory, cardiovascular, musculoskeletal, nutritional, psychological), and improving exercise tolerance and quality of life (Reis, 2001). Conventional treatment of moderate to severe COPD according to the recently developed global strategy by the GOLD Scientific Committee for the diagnosis, management, and prevention of COPD, includes smoking cessation and regular use of inhaled medications including short and long acting beta agonists and anticholinergic agents. Inhaled or systemic glucocorticoids are used if there is proven benefit according to lung function response and significant symptom relief/improvement. An additional oral bronchodilator (methylxanthine or theophylline derivative) is sometimes used if there are no contraindications (Pauwels, Buist, Ma, Jenkins, Hurd, & GOLD Scientific Committee, 2001). Long term oxygen therapy, which has demonstrated increased survival benefit (Nocturnal Oxygen Therapy Trial Group, 1980) is required to manage hypoxia associated with disease progression in moderate to severe, advanced COPD. With disease progression however, patients with severe stable COPD who lack the necessary respiratory reserve to respond to minimal increases in ventilatory demand (due to their altered dynamics including; reduced alveolar ventilation, dynamic hyperinflation and increased inspiratory work of breathing), are constantly on the verge of respiratory decompensation.

Restrictive Pulmonary Disorders

Patients with neuromuscular syndromes, including amyotrophic lateral sclerosis (ALS), Guillain Barré Syndrome, postpolio syndrome, myasthenia gravis, multiple sclerosis, muscular and myotonic dystrophies, develop phrenic nerve impairment, diaphragmatic and intercostal muscle weakness, and in some cases eventual pharyngeal muscle involvement, leading to reduced alveolar ventilation and gas exchange and impaired ability to clear airway secretions. The development of pharyngeal muscle weakness can contribute to upper airway collapsibility, placing patients at risk for aspiration and recurrent respiratory infection. Severe thoracic deformities such as scoliosis and kyphoscoliosis, resulting in restrictive pulmonary disease, also result in impaired alveolar ventilation and chronic respiratory failure. Intercostal muscle and diaphragmatic dysfunction result in reduced lung volumes, increased collapsibility of airways, pulmonary atelectasis, and retained secretions. Sleep fragmentation, nightmares, morning headaches, increasing daytime fatigue and hypersomnolence in patients with neuromuscular syndromes signal nocturnal hypoventilation, worsening gas exchange and sleep disordered breathing associated with the subsequent development of hypoxic and hypercapnic respiratory failure in progressing neuromuscular disease (Barthlen, 1997; Unterborn & Hill, 1994).

Treatment strategies common to most restrictive pulmonary disorders are generally directed toward optimizing hydration, nutrition, and mobility, management of psychosocial issues including anxiety and depression, facilitation of secretion clearance and early intervention for upper respiratory tract infections. Monitoring of lung function, nocturnal oximetry and arterial blood gases assist in the assessment and management of associated respiratory failure. With the development of daytime symptoms of somnolence, dyspnea, fatigue, or morning headache, in conjunction with hypercapnia, nocturnal oxygen desaturation, reduced maximal inspiratory pressure and forced vital capacity, NIPPV is often used as a temporizing therapeutic short term treatment option to prolong survival, ameliorate distressing symptoms, and improve gas exchange (Mehta, & Hill, 2001; Annane, Chevrolet, Chevret, & Raphael, 2002).

Management of Chronic Respiratory Failure

Regardless of the mechanisms underlying COPD or restrictive pulmonary disorders, both result in the eventual development of chronic respiratory failure characterized by varying degrees of ventilation perfusion mismatch, hypoxia, hypercapnia, and sleep disordered breathing (McNicholas, 1997). Reduced respiratory reserve renders patients with chronic respiratory failure due to COPD and restrictive pulmonary disorders at risk for acute respiratory decompensation (Murata, Kapsner, Lium, & Busby, 1998; Unterborn & Hill, 1994). Symptom management and prevention of respiratory decompensation resulting in acute on chronic respiratory failure, are important in reducing morbidity and mortality associated with COPD and restrictive pulmonary disorders.

Within the last few decades, varying options for different forms and modes of mechanical ventilation have been developed. Delivery of bilevel positive pressure ventilation noninvasively by nasal, orofacial, or full face mask to assist ventilation is now possible. Bilevel positive airway pressure ventilation, which includes both inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP), has been shown to decrease work of breathing (Vanpee, Kawand, Rousseau, Jamart, & Delaunois, 2002). Bilevel NIPPV has also been shown to increase lung volume during use (Ambrosino, Nava, Bertone, Fracchia, & Rampulla, 1992), which is believed to result in improved alveolar recruitment and ventilation, contributing to reduced ventilation perfusion mismatch and improvement in gas exchange (Meyer & Hill, 1994). Bilevel NIPPV has been used to assist in the management of both acute and chronic respiratory failure due to chest wall deformities and neuromuscular diseases resulting in restrictive pulmonary disorders (British Thoracic Society, 2002; Meduri, 1996; Meyer & Hill, 1994). Bilevel NIPPV has been shown to be effective in the management of acute on chronic respiratory failure in hemodynamically stable patients with COPD and restrictive pulmonary disorders who do not wish to undergo invasive mechanical ventilation (Lightowler, Wedzicha, Elliott, & Ram 2003; Mehta & Hill, 2001; Ram, Lightowler, & Wedzicha, 2003). The use of bilevel NIPPV in acute on chronic respiratory failure due to COPD exacerbation (where there is a reversible component) has been shown to reduce the need for intubation and mechanical ventilation, and reduce length of hospital stay and mortality (American Thoracic Society, 1995; British Thoracic Society Standards of Care Society, 2002; Meduri, 1996; Meyer & Hill, 1994). Evidence to support the use of bilevel NIPPV in the setting of chronic respiratory failure due to stable COPD however, has been inconsistent (Casanova, Bartome, Tost, Soriano, Abreu, Velesco, & Santoralio, 2001; Hill, 2000; Rossi, 2000). Furthermore, although bilevel NIPPV is generally introduced as symptoms of hypoventilation, impaired gas exchange and increased work of breathing associated with worsening chronic respiratory failure arise in restrictive pulmonary disorders, existing evidence regarding a therapeutic role is weak and there is inconclusive evidence to support any sustained improvement in inspiratory muscle strength in patients with restrictive pulmonary disorders (Annane, Chevrolet, Chevret, & Raphael, 2002). Furthermore, existing systematic literature reviews regarding the management of chronic respiratory failure due to COPD and restrictive pulmonary disorders are not specific to bilevel NIPPV (Mehta & Hill 2001; Annane et al. 2002).

Purpose of the Study

The purpose of this systematic literature review was to critically appraise and summarize existing studies involving the effectiveness of bilevel NIPPV in the management of chronic respiratory failure in COPD and restrictive pulmonary disorders. The specific questions addressed were:

1. What is the nature and extent of the effectiveness of bilevel NIPPV in the management of chronic respiratory failure associated with COPD and restrictive pulmonary disorders?

2. What is the nature and extent of the supportive role for bilevel NIPPV in the management of chronic respiratory failure associated with COPD and restrictive pulmonary disorders?
3. What is the nature and extent of bilevel NIPPV use in the preventative management of patients with chronic respiratory failure due to COPD and restrictive pulmonary disorders?
4. What is the nature and extent of bilevel NIPPV use in altering the progression of chronic respiratory failure due to COPD and restrictive pulmonary disorders?
5. What is the difference in the nature and extent of the response to bilevel NIPPV use in different subsets of the COPD and restrictive pulmonary population with chronic respiratory failure?

Significance of the Study

This systematic review examines the effectiveness of bilevel NIPPV in the management of chronic respiratory failure due to COPD and restrictive pulmonary disorders. Unlike existing reviews, this study includes both randomized controlled trials (RCTs) and observational studies with post intervention follow-up of less than, as well as greater than 3 months. Since changes in technology related to modes of bilevel NIPPV as well-as mask interfaces have occurred over time, this review identifies and summarizes adverse events related to noncompliance affecting this intervention.

This systematic review also assesses the effectiveness of bilevel NIPPV with respect to a preventative role in slowing the progression of worsening gas exchange, lung function, sleep quality/quantity, and distressing symptoms (dyspnea, WOB, exercise tolerance) related to worsening CRF due to COPD and restrictive pulmonary disorders.

The nature and extent of a supportive role for bilevel NIPPV in rendering disease related morbidity more manageable for patients with chronic respiratory failure and reduced respiratory reserve due to COPD and restrictive pulmonary disorders, is assessed, according to dyspnea, altered health related quality of life (HRQOL), repeated exacerbations, and compromised functional levels that patients constantly strive to cope with as they attempt to gain control over the limitations that progressive CRF imposes on their lives.

Chapter Two

Methods

Criteria for Considering Studies for Review

Types of Studies

This systematic literature review included randomized controlled trials (RCTs) and observational studies involving adults with COPD and restrictive pulmonary disorders who received bilevel NIPPV as an intervention for chronic respiratory failure.

Study Participants

Participants enrolled in the studies included adults (18 years and older) with chronic respiratory failure due to COPD (chronic bronchitis, emphysema), or restrictive pulmonary disorders resulting from neuromuscular disorders (amyotrophic lateral sclerosis, polio, post-polio syndrome, Guillian-Barré syndrome, muscular dystrophy, myasthenia gravis), and skeletal restrictive thoracic wall deformities (kyphoscoliosis, thoracoplasty). For the COPD cohort, studies in which subjects were predominantly asthmatic and/or had reversibility of airflow obstruction according to pulmonary function, were excluded. Chronic respiratory failure (CRF) was defined by the physiological changes compatible with underlying COPD or restrictive pulmonary disorders, arterial blood gases, declining lung function, symptoms of chronic hypoventilation, increased work of breathing, dyspnea, and reduced exercise tolerance.

Study Intervention

Studies were included that employed the use of bilevel NIPPV via nasal, oronasal (mouth and nose), and/or oronasofacial (entire face) mask interfaces as an intervention to manage derangements in arterial blood gases, lung function, and symptoms associated with worsening CRF.

Study Outcome Measures

The primary outcome was respiratory function as assessed by:

1. gas exchange (arterial blood gases, $Sa0_2$, $PtC0_2$).
2. lung function (FEV1, FVC, FEV1/FVC, TLC).
3. ventilatory/breathing pattern (VE, VT, Ti, ti/Ttot, Ttot).
4. respiratory muscle function/work of breathing (MIP, MEP, EMGdi, EMGst, PEEPidyn, Pdi, PImax, PEmax, PI, PTPdi, Wdi, Wdi/min, WOB/min).

Health-related outcomes were assessed as secondary outcomes and included:

1. symptom relief (dyspnea, morning headache, daytime somnolence, fatigue, sleep).
2. functional status (BiPAP Functional Impairment Scale, LCADL, MMRCD, Oxygen Cost Diagram).
3. exercise tolerance (6MWT, SWT).
4. health-related quality of life (CRDQ, MRF-28, SF-36, SGRQ).
5. morbidity (hospital admissions, ICU admissions, hospital length of stay).
6. mortality (survival estimates).

Comfort/compliance issues were also noted.

Search Strategies for Identification of Studies

Detailed search strategies were developed for each database used to identify published studies for inclusion in the systematic review. The search terms employed were bilevel, bi-level airway pressure OR bi-level CPAP OR biphasic positive airway pressure, as well as nasal ventilation, OR positive pressure ventilation OR NIPPV. Electronic databases searched included MEDLINE, preMEDLINE, EMBASE, CINAHL, Conference Papers Index, OCLC Papers First (Conference Papers), Cochrane Library (including Cochrane Database of Systematic Reviews, DARE, Cochrane Controlled Trials), ACP Journal Club, Pubmed, Biological Abstracts, and Dissertation Abstracts for the years 2001 to 2003. The following Journals were hand-searched for the years 2001 – 2003: *American Journal of Respiratory Critical Care Medicine, Chest, European Respiratory Journal, Lung, The New England Journal of Medicine, and Thorax.* Reference lists of all relevant articles identified for inclusion in this systematic review were manually screened to identify any additional studies. Only English studies were included.

Review of the Studies

Study Selection

The titles and abstracts (when available) of all published reports identified through the electronic search were scanned independently by this reviewer and one other reviewer. For studies that appeared to meet the inclusion criteria, or for those for which there was insufficient data in the title and abstract to make a decision, the full study reports were obtained. The full study reports were then assessed independently by the two reviewers to establish whether the studies met the inclusion criteria. Disagreements were resolved by consensus.

Quality Assessment

The assessment of the quality of all included studies was undertaken independently by the two reviewers. Quality criteria examined for RCTs followed the

Randomized Controlled Trial (RCT) Validity Tool developed by Estabrooks, Goel, Thiel, Pinfold, Sawaka, and Williams (1999) (Appendix A and B) that included:

- design allocation
- recruitment
- inclusion and exclusion criteria
- description of intervention
- statistical analysis and outcome measurement

Quality criteria examined for observational studies followed the Observational Study Validity Tool developed by Estabrooks et al. (1999) (Appendix C and D) that included:

- design allocation
- inclusion and follow up
- control of confounders
- data collection
- outcome measurement
- statistical analysis
- conclusion and discussion

The methodological quality of the studies was then estimated as low, med, or high.

Data Extraction

Data extraction was carried out for each study included using a data extraction form designed for this systematic review (Appendix E, F, and G). The data extraction form was piloted on several studies and modified as required before use. Data extracted included:

- Year of publication, country of origin, language, sponsorship, author's name/s, title of study.
- Study characteristics including setting, design, sample size.
- Details of study participants including demographic characteristics, criteria for inclusion/exclusion, description of withdrawals and drop-outs.
- Description of study groups and intervention employed.
- Description of outcomes reported, including method of assessment, and any adverse events reported.
- Description of data analysis techniques and reported findings.
- Notation of missing data.

Data Analysis

Data were analyzed for each of the COPD and restrictive pulmonary cohort studies first, by assessing heterogeneity to determine the appropriateness of pooling the data. Clinical heterogeneity was assessed by examining differences in study quality, participants, interventions, and measurement of outcomes of each study. Statistical heterogeneity was assessed using both a fixed and random effects model, with $p<0.05$ considered statistically significant. For data that were too heterogeneous to proceed with statistical aggregation, a narrative qualitative summary was reported. Where meta-analysis was possible for RCTs, weighted mean differences (WMD) and 95% confidence intervals (CI) were calculated using the Revman 4.2 statistical package for the following comparisons:

1. RCTs of bilevel NIPPV intervention versus all modalities (LTOT, Sham ventilation, Exercise).

2. RCTs of bilevel NIPPV intervention versus all modalities by length of trial, with subgroup analysis for trials 8 weeks or > 8 weeks.

Meta-analysis for within-subject crossover studies was also done, comparing bilevel NIPPV intervention versus all modalities (LTOT, Sham ventilation, Exercise). To facilitate meta-analysis for within-subject crossover studies, the mean difference (MD) and standard error (SE) for each study outcome were first calculated in Excel, then entered into Revman 4.2 statistical package under the generic inverse variance outcome to calculate the mean difference. Subgroup analyses were not done for the within-subject crossover studies.

Categorical treatment effects were pooled using a random effects model and reported as mean differences, with 95% confidence intervals. Continuous treatment effects were pooled using a random effects model and reported as the mean difference, with 95% confidence intervals. A random effects model, which takes into consideration variation of study differences in underlying effect, was used for calculation of the overall effect.

Chapter Three

Findings

Description of Studies Included in the Systematic Review

Using the search terms for this systematic literature review, a multiple database search was conducted (with duplicates excluded) for the years 1980 to 2003.The search was initially done in February 2003 and repeated again in December 2003. There was a total of 4084 and 205 hits from the February and December database searches, respectively. The number of hits per database is displayed in Tables 1 and 2 for a detailed search summary.

There were a total of 368 abstracts identified from the database searches in February and December collectively. From these, 203 abstracts were excluded (duplicate abstracts; those that included acute respiratory failure, invasive ventilation, modes of NIPPV that were not bilevel, i.e. CPAP, volume ventilation, negative pressure ventilation; and non-English studies). Of the 177 abstracts remaining, there were 55 COPD studies, 86 restrictive pulmonary disorder studies, and 35 mixed studies (including both COPD and restrictive pulmonary disorders). The 177 full reports were then obtained, and independently screened for inclusion by the two reviewers. The total number that met the inclusion criteria was 32 studies (see Table 3). Of the 32 studies that were included in this systematic review, 22 were COPD studies, 8 were restrictive pulmonary disorder studies, and 2 were mixed studies.

From a historical perspective, there were 12 studies for the period 1980 to 1989 (11 restrictive and 1 mixed), none of which met the inclusion criteria for this review. There were no COPD studies for this time period retained during the search.

The greatest number of abstracts (115) were identified for the years 1990 to 1999 (40 COPD, 48 restrictive, and 27 mixed). Only 20 of the studies from this time period met the inclusion criteria (13 COPD, 5 restrictive, and 2 mixed). Fifty abstracts were identified from 2001 to 2003 (16 COPD, 25 restrictive, and 9 mixed); 12 studies met the inclusion criteria (9 COPD and 3 restrictive).

Study Designs

There were 6 RCTs included in this systematic review, all with COPD cohorts. The remaining 26 observational studies consisted of within-subject crossover, within-subject non-crossover, and nonequivalent group designs. Ten of the observational studies used a within-subject crossover design (2 before/after and 8 repeated measures) and were primarily with COPD cohorts, with the exception of one mixed before/after crossover study. There were 3 COPD nonequivalent group studies (one before/after and two repeated measures). The remaining observational studies consisted of 1 COPD and 3 restrictive within-subject before/after studies, 3 COPD and 5 restrictive within-subject repeated measures studies (see Tables 4, 5, and 6).

Sixteen of 22 COPD studies included a run-in or acclimatization period, which varied in length from 2 hours to one month and 10 days. Six of the COPD studies did not include a run-in or acclimatization period. Half of the restrictive studies did not involve a run-in or acclimatization period, 2 studies included in-hospital bilevel NIPPV titration, and the remaining 2 studies had a run-in or acclimatization period of 3 days and one month, respectively. The 2 mixed studies reported 3 hour and 3 night acclimatization periods, respectively (see Tables 4, 5, and 6).

Study Participants

Study participants from the COPD studies were chronically dyspneic and had severe obstructive lung disease, with a baseline FEV1 less than 1 liter and FEV1/FVC ratio less than 50% of predicted (see Tables 7 and 8). Subjects in 3 of the 6 RCTs were hypoxic with a baseline PaO_2 less than 60 mmHg on room air, while 5 out of the 6 RCTs included hypercapnic subjects with baseline $PaCO_2$ greater than 50 mmHg. Study participants from 4 of the 9 COPD within-subject crossover studies had a baseline PaO_2 greater than 60 mmHg, with a baseline $PaCO_2$ greater than 50 mmHg in 8 of the studies. Subjects in the remaining within-subject before/after, within-subject before/after repeated measures, and nonequivalent group studies had a baseline PaO_2 less than 55 mmHg, with the exception of one study, in which the baseline PaO_2 was 68.1 mmHg. The baseline $PaCO_2$ of subjects in these studies was greater than 50 mmHg in all except one study, with a $PaCO_2$ of 42.2 mmHg (see Tables 4 and 5).

Lung function in the all of the restrictive cohort studies also showed significant impairment, with markedly reduced baseline FVC less than 50% predicted. $PaCO_2$ was 45 mmHg or greater in all except one study. Subjects in the restrictive studies had symptoms of nocturnal hypoventilation including hypersomnolence, morning headache, and daytime fatigue. All subjects had chronic respiratory failure resulting from kyphoscoliosis, post-tuberculosis sequelae, or neuromuscular disease (see Tables 5 and 8).

Participants in the COPD studies had a mean age of 63 years and older, with a mean age range of 47 to 71 years. The mean age range for the restrictive study participants was 18.3 to 66.2 years. There was a predominance of male subjects in all of the COPD studies, 7 of the 8 restrictive studies, as well as in the mixed studies. Two of the COPD studies included only males (see Tables 10, 11, and 12).

Sample size for each of the studies in this systematic review are small, with less than 20 subjects in 20 of the 32 studies, and less than 50 in all but 2 studies. The total combined sample size was 513 for the COPD studies, 117 for the restrictive studies, and 26 for the mixed studies (see Tables 10, 11, and 12).

Study Length of Follow-up

Length of the follow-up for the 6 COPD RCTs varied from 5 days to 2 years. Three RCTs included follow-up of 8 weeks or less (5 days, 3 weeks, and 8 weeks), and 3 RCTs were longer than 8 weeks (3 months, 1 and 2 years). Six of the 9 COPD crossover studies were short daytime trials of 1 to 3 days, while the remaining 3 were longer nocturnal trials (6 weeks, 3 and 6 months). Of the remaining COPD studies (within-subject before/after, within-subject repeated measures, and nonequivalent groups), 6 were less than one week, 1 was 4 weeks, and the longest was 3 years. Of the restrictive studies (within-subject before/after and within-subject repeated measures), 2 studies were trials of 1 week or less, 2 were 1 to 6 weeks, and 4 were 6 weeks or longer. The 2 mixed studies (within-subject crossover and within-subject before/after) had trials of less than 1 week. The majority of the shorter trials of 1 week or less tended to be daytime studies, while the longer trials were all nocturnal studies (see Tables 4, 5, and 6).

Study Comparisons

Study comparisons for the COPD RCTs were varied; bilevel NIPPV versus spontaneous breathing, bilevel NIPPV versus sham ventilatilation, bilevel NIPPV and LTOT versus LTOT, bilevel NIPPV and exercise versus exercise (2 studies), bilevel

NIPPV versus other types of ventilation, i.e., negative pressure ventilation, volume ventilation (4 studies), different bilevel NIPPV pressure settings (4 studies), different types of bilevel NIPPV ventilators (2 studies). Comparisons for the restrictive studies were less varied and included only bilevel NIPPV versus spontaneous breathing (6 studies), bilevel NIPPV and exercise versus exercise (2 studies), and different types of bilevel NIPPV ventilators (one study). Mixed studies compared bilevel NIPPV versus other types of ventilation (one study), and one study compared different bilevel NIPPV modes, i.e., spontaneous versus spontaneous timed (see Table 13).

Study Interventions

All COPD studies used a Respironics BiPAP for the NIPPV intervention except the study by Nava (1993), which used a BIRD PSV ventilator, and the study by Highcock (2003), which compared three types of NIPPV (BiPAP Respironics ST 30, Nippy2, VPAP II ST models). In 10 of the 21 COPD studies that used BiPAP Respironics, the Spontaneous (ST) mode was used, while 9 of the remaining studies used the spontaneous (S) mode. Seven of the 22 COPD studies used an IPAP of 10 cmH_20 or less and 9 reached IPAP pressures of 20 cmH_20 or greater. EPAP pressures were 5 cmH_20 for all the COPD studies except the study by Vanpee (2002a), in which EPAP pressures of 5 and 10 cmH_20 were used. Five of the 8 restrictive studies used BiPAP Respironics NIPPV (S mode for 2 studies, ST mode for 2 studies, and a timed (T) mode for one study. Of the remaining restrictive studies, other pressure targeted ventilators were used for NIPPV including Sullivan VPAP and Quantum PSV NIPPV for one study, a DP-90 (Taema, France) ventilator for another study, and a Moritz II Bilevel ventilator for another study (see Tables 7, 8, and 9).

A nasal interface was used in 19 of the 22 COPD studies, oronasal interface in one study, and nasal, oronasal, and fullface masks in one study. A nasal interface was used in all but one restrictive study, which used a mouthpiece. The 2 mixed studies used a nasal interface.

Six of the COPD studies included the use of oxygen in some but not all participants, all subjects used oxygen in 9 of the COPD studies, 4 studies did not include oxygen use, and 2 studies did not report oxygen use. Four restrictive studies used oxygen for some of the participants, one study included oxygen use for all participants, one did not include oxygen use, and 2 studies did not report on oxygen use. Oxygen was used in one mixed trial and not in the other (see Tables 7, 8, and 9).

Study Outcome Measures

Outcome measures reported in the studies include gas exchange ($Pa0_2$, $PaC0_2$, nocturnal oxygen saturation, and $PetC0_2$/trancutaneous $C0_2$); lung function (FEV1, FEV1/FVC ratio for COPD and mixed studies, and FVC for restrictive studies); ventilation/breathing pattern (VE, Vt, Ttot, Ti/Ttot, VT/Ti); respiratory muscle function/work of breathing (EMGdi, MIP, MEP, PTPdi, Pdi, PEEPidyn, PImax, Pemax, RL, ELdyn, Wdi, WOB); exercise tolerance (6MWT, SWT), sleep (SE, SL, SQ, TST); dyspnea (ATS, BORG, dyspnea portion of CRDQ, MRSC, VAS, and Dyspnea Scale of Mahler) and symptom relief; functional status (MMRCD, Oxygen- cost Diagram, BiPAP Functional Impairment Scale, LCADL); HRQOL (CRDQ, MRF-28, SGRQ, SF-36); morbidity (hospital, ICU admissions); mortality (survival rate); and comfort/compliance (reasons for noncompliance to bilevel NIPPV).

Gas exchange was the most frequently reported outcome measure and was reported in all COPD RCTs and within-subject crossover studies, except 2 recent COPD studies from 2002, which focused on respiratory muscle function, work of breathing, and ventilatory pattern (Vanpee 2002a; Vanpee 2002b). All restrictive studies included gas exchange as an outcome measure, as well as the 2 mixed studies. A total of 10 COPD studies (5 RCTs, 3 within-subject crossover, and 2 other observational studies) and 6 restrictive studies assessed lung function in response to bilevel NIPPV.

Respiratory muscle function/work of breathing was the next most frequently reported outcome measure in 14 out of 22 COPD studies (5 RCTs, 5 within-subject crossover, and 4 other observational studies), of which 8 were between 2000 and 2002. Three out of 8 restrictive studies reported on this outcome measure. Ventilatory/breathing patterns were studied in 11 COPD studies (1 RCT and 5 within-subject crossover trials, and five other studies), 6 of which were between 2000 and 2003, and 2 restrictive studies from 1990 and 2002.

Dyspnea was the next most frequently reported outcome measure in 8 COPD studies (4 RCTs from 1994, and 2000 to 2002; 4 observational studies from 1991 to 1998, and one in 2002). Four restrictive studies reported dyspnea ratings; 3 from 1992 to 1996 and one from 2002. Exercise tolerance was reported in 9 COPD studies (4 RCTs from 1994 to 2003, 2 within-subject crossover and 3 other observational studies between 1995 and 2003), and 2 restrictive studies both from 2002. General symptom improvement in the form of patient report by questionnaire (reduced daytime somnolence, headache, morning fatigue, concentration, nightmares) was described in 3 restrictive studies from 1992 to 1997. Two COPD studies (1991 and 2000) included neuropsychological testing which assessed 10 different measures including attention, memory, constructional praxis, and psychomotor coordination.

Various sleep characteristics (sleep efficiency, latency, quality, and/or total sleep time) were reported for 6 COPD studies (2 RCTs and 4 within-subject crossover), 5 that were from the 1990's and one from 2002. Two restrictive studies (1992 and 2002) and 2 mixed studies (1993 and 1995) assessed sleep as an outcome.

One of the least studied outcomes related to bilevel NIPPV intervention for management of chronic respiratory failure, included health-related quality of life (HRQOL), with a total of 2 COPD RCTs from 2000 and 2002, 1 COPD within-subject crossover study from 1995, and one restrictive study from 1996. Functional status/ADL outcome was found in only 2 COPD RCTs from 1994 and 2000. Morbidity in terms of hospital and ICU admissions was reported in 2 COPD RCTs from 2000 and 2002, and 1 COPD observational study from 1998. Only 1 restrictive study from 1996 reported on morbidity. Mortality rate was reported for 2 COPD RCTs from 2000 and 2002, and 1 COPD observational study from 1998.

Methodological Quality of Studies in the Review

Randomized Controlled Trials

Using criteria based on the RCT Validity Tool developed by Estabrooks et al. (1999), the overall quality rating for 5 out of the 6 RCTs was high (Clini, 2002; Casanova, 2000; Diaz, 2002; Garrod, 2000; Gay, 1996), with 1 RCT (Renston 1994) rated as medium (see Table 14). Although all 6 RCTs in this systematic review provided information regarding randomization, only 4 of the 6 studies provided information that was sufficient to adequately determine if blinding of randomization occurred (Clini, 2002; Casanova, 2000; Diaz, 2002; Garrod, 2000). The description of randomization in the remaining 2 RCTs was not sufficient to preclude that blinding of randomization actually occurred (Gay, 1996; Renston, 1994). None of the studies were double-blind with respect to interventions, however three of the studies, which were single-blind, did attempt to incorporate concealment of treatment intervention/allocation through the use of bilevel NIPPV in the treatment group and sham ventilation in the control group (Diaz, 2002; Gay, 1996; Renston, 1994). Bilevel NIPPV intervention was not able to be masked in the remaining studies, which compared bilevel NIPPV to 'standard care', bilevel NIPPV and long term oxygen therapy (LTOT) versus LTOT alone, and bilevel NIPPV and excercise versus exercise program alone, respectively (Casanova, 2000; Clini, 2002; Garrod, 2000). The study by Diaz (2002), which used sham ventilation, reported blinding of the intervention to physicians responsible for the patients' care, however it is not clear that the intervention was blinded to researchers (Diaz, 2002). The study by Clini (2002) incorporated blinding of outcome measures assessed.

Sample size at initial evaluation, at randomization, and on follow-up, were reported for all 6 RCTs. Despite attrition in most of the RCTs (5 out of 6 which were longer studies), study groups for each RCT maintained fairly equal numbers of participants from randomization to completion of the study in 4 out of 6 RCTs (see Table 10). Attrition rates were less than 20% for 4 of the RCTs (Casanova, 2000; Diaz, 2002; Garrod, 2000; Renston, 1994), and higher in the studies by Clini (2002) and Gay (1996) (54% and 23%, respectively). Four out of 6 of the RCTs assessed sample size via power analysis, for an effect size required to achieve 80% power at 5% level of significance (Casanova, 2000; Clini, 2002; Diaz, 2002; Garrod, 2000).

There were a number of intervening variables that may have confounded measurement of study outcomes. Some studies included an acclimatization period, during which participants could familiarize themselves and become comfortable on NIPPV prior to initiation of the study (Casanova, 2000; Clini, 2002; Garrod, 2000), while shorter studies did not (Renston, 1994). Some but not all patients in every study group used oxygen (Casanova, 2000; Garrod, 2000; Gay, 1996). Longer studies were either started in the inpatient setting, then completed with the patient at home with phone and/or outpatient clinic follow-up, with accuracy and extent (use) of treatment intervention/compliance relying more heavily on subjects' self-reports (Casanova, 2000; Clini, 2002; Garrod, 2000; Gay, 1996). Hours of use, time of day, and length of each trial varied among the studies, as did bilevel NIPPV IPAP/EPAP settings.

Crossover Within-subject Studies

Eight of the 10 within-subject crossover studies had an overall high quality rating (Highcock, 2003; Lien, 1993; Lin, 1996; Krachman, 1997; Marangoni, 1997; Meecham-Jones, 1995; Nava, 1993; Strumpf, 1991), while the remaining 2 studies (Ambrosino, 1992; Elliott, 1995) had an overall medium quality rating, based on assessment criteria from the Observational Study Validity Tool developed by Estabrooks et al. (1999). Two of the studies that had attrition rates of over 20% were longer studies (Meecham-Jones, 1995; Strumpf, 1991), while five that had no attrition rate were shorter studies (Elliott, 1995; Highcock, 2003; Krachman, 1997; Lien, 1993; Marangoni, 1997). The majority of the within-subject crossover studies used a repeated measures design (8 out of 10 studies), while two were before/after designs. All of the studies included random assignment and statistically attempted to control for confounders, with 9 out of 10 studies including assessment of subject equivalence in their analysis. All of the within-subject crossover trials were COPD studies, except for 1 mixed study (see Table 14).

Non-crossover Studies

There were 8 within-subject non-crossover repeated measures studies; 4 that were short COPD studies (Ambrosino, 1993; Bianchi, 1998; Vanpee, 2002b; Vitacca, 2000) and 5 restrictive pulmonary studies (Highcock, 2002; Hill, 1992; Fanfulla, 1997; Nauffal, 1996; Waldhorn, 1992). Six of these 8 studies had a high overall quality rating and 2 had a medium quality rating (see Tables 15 and 16). In 3 of the 8 within-subject non-crossover repeated measures studies (Bianchi, 1998; Highcock, 2002; Vitacca, 2000), random order assignment of the treatment interventions (i. e., different bilevel pressure levels, different types of bilevel noninvasive positive pressure ventilators) was used. Four of the 8 studies were conducted in a tertiary setting, while the remaining outpatient studies had the initial NIPPV acclimatization done in a controlled secondary or tertiary setting prior to outpatient bilevel NIPPV. All of the within-subject non-crossover studies statistically attempted to control for confounders. The longest studies, 18 months and 2 years in length respectively, had attrition rates of 16% (Nauffal, 1998) and 30% (Fanfulla, 1997), while the remaining shorter studies (including a 7 week study by Hill, 1992) had no attrition (see Table 12).

Four out of a total of 5 within-subject before/after studies had medium to high quality ratings (Ambrosino, 1993; Ergun, 2002; Highcock, 2002; Restrick, 1993) and were conducted in a controlled tertiary or secondary setting, using random order assignment of NPSV sessions (Tables 15 and 16). The remaining study, which had a low quality rating, was done in an outpatient setting with home and clinic follow-up (Strump, 1990). This study had a varied length of bilevel intervention in a sample of 4 subjects, and did not include any statistical control of confounders (see Table 15 and 16).

There were 3 nonequivalent group studies (2 repeated measures and 1 before/after), which were all COPD studies (Vanpee, 2002a; Nava, 1993; Clini, 1998). Two of the 3 studies (Clini, 1998; Nava, 2001) had a high quality rating, while the third study (Vanpee, 2002) had a medium rating.

All the studies in this systematic review were strong with respect to description of inclusion and exclusion criteria and interventions. The majority attempted to clinically and statistically control for confounders in a cohort with advanced chronic obstructive or restrictive pulmonary disease and attendant CRF (see Tables 15 and 16). Sample sizes were small (see Tables 10, 11, and 12), with less than 50 subjects completing all but one study in the review, which had 52 subjects at the time of completion (Nauffal, 1996).

Results

There were 22 COPD studies included in this systematic review, with a total of 399 adults with severe stable COPD that completed trials; 8 restrictive studies, with a total of 104 subjects that completed trials; 2 mixed studies with a total of 26 subjects that completed trials. The study comparisons for the COPD and restrictive studies were varied: bilevel NIPPV versus spontaneous breathing or sham/placebo ventilation; bilevel NIPPV with longterm oxygen therapy (LTOT) versus LTOT; bilevel NIPPV versus other types of ventilation (negative pressure, volume ventilation); bilevel NIPPV with exercise versus exercise alone; different bilevel pressure settings; different types of bilevel ventilators; different bilevel modes (S, ST) (see Table 13). The 2 mixed studies assessed bilevel versus other types of ventilation and different bilevel modes. The varied comparisons, study designs, and different measures for some of the outcomes amongst the COPD studies in this systematic review limited which studies could be combined for meta-analysis. An attempt was made to include both NIPPV versus all modalities, as well as meta-analysis of subgroups according to study comparisons for a particular outcome.

COPD Studies

Gas Exchange. Data obtained from 2 or more of the 6 RCTs were combined where the measures were similar for a particular outcome, and meta-analysis conducted. All 6 RCTs assessed gas exchange using $Pa0_2$ mmHg and $PaC0_2$ mmHg as outcome measures for a total of 191subjects. Outcomes for $Pa0_2$ mm Hg (WMD = 1.86, 95% CI -0.60 to 4.32) and $PaC0_2$ mm Hg (WMD = -1.20; 95% CI -5.05 to 2.65) slightly favoured bilevel NIPPV, although not statistically significant (see Figures 1 and 2). Using the generic inverse variance and mean difference and standard error, meta-analysis of 7 within-subject crossover studies significantly favoured an effect for improved $Pa0_2$ with bilevel NIPPV in a total of 131 subjects, based on both a fixed (MD = 3.27, 95% CI 1.49 to 5.05; p = 0.0003) and random effects model (MD = 4.49, 95% CI 1.43 to 7.55; p = 0.004) (see Figure 3). The six RCTs also failed to show evidence for a reduction of $PaC0_2$ with bilevel NIPPV on combined analysis (WMD = -1.20, 95% CI -5.05 to 2.65).

Eight within-subject crossover studies with a total of 153 subjects, favored bilevel NIPPV for $PaC0_2$ reduction with statistical significance based on random (MD = -3.52, 95% CI -5.93 to -1.11) and fixed models (MD = -3.14, 95% CI -4.87 to -1.40) (see Figure 4). However, heterogeneity was evident based on p values of 0.13 for both models. Removing the study by Strumpf (1991) reduced, but did not eliminate, the heterogeneity. Subgroup analysis of the RCTs for $Pa0_2$ and $PaC0_2$ also showed no evidence for improved gas exchange according to trial length of less than/equal to, or greater than 8 weeks, respectively (see Figures 5 and 6).

Of the before/after, repeated measures, and nonequivalent group COPD studies, there were five that assessed gas exchange. Two of the studies (Ambrosino, 1993; Vitacca, 2000) showed statistically significant increases in PaO_2 and decreases in $PaCO_2$ ($p < 0.01$ for both values in both studies) and two studies (Clini, 1998; Nava, 2001) showed improvements in PaO_2 and $PaCO_2$ that did not reach statistical significance. The fifth study (Bianchi, 1998) assessed the response of hypercapnic COPD patients using CPAP, bilevel PSV, and PAV modes compared to sham ventilation with exercise, and showed a statistically significant decrease in $PETCO_2$ ($p < 0.05$) (see Table 17).

Lung Function. There was no evidence to support a statistically significant improvement of FEV1 with bilevel NIPPV in the 5 RCTs, or the within-subject crossover COPD studies (see Figures 7 and 8). Three of the 5 RCTs showed a slight increase in FEV1 (Casanova, 2000; Clini, 2002; Diaz, 2002), while 2 others reported a slight decrease in FEV1 (Garrod, 2000; Gay, 1996). There was a statistically significant increase in FVC by 9% in one RCT (Clini, 2002). There were also 2 nonequivalent group COPD studies, one which reported a slight but not statistically significant increase in FEV1 and FVC (Nava, 2001), and one which reported no significant change over time (Clini, 1998) (see Tables 18 and 19).

Two RCTs included residual volume (RV) as part of an assessment of dynamic hyperinflation. Casanova (2000), which compared bilevel NIPPV and LTOT to LTOT alone, reported no change in RV, while Diaz, (2002) compared bilevel NIPPV to sham ventilation, and reported a significant reduction in RV from $201 \pm 48\%$ predicted to

165±49)% predicted ($p < 0.001$), following 3 weeks of bilevel NIPPV. RV in that study with sham ventilation increased from 201±55% predicted to 209±51% predicted.

Ventilatory/Breathing Pattern. One of the 6 RCT studies (Diaz, 2002) with 36 subjects, assessed changes in pattern of breathing with high inspiratory pressures (IPAP 18±2 cmH_20/EPAP min of 2 cmH_20) via bilevel versus sham NIPPV (CPAP) in patients with stable hypercapnic COPD during exercise. This study found significant increases in VE ($p < 0.05$; 1.16 L/min increase), VT ($p < 0.001$; 181 ml increase), and Ttot ($p < 0.01$; 0.67 second increase) during bilevel ventilation, which were associated with reduced RV, TLC, and PEEPidyn, in keeping with reduced lung hyperinflation and subsequent reduction in work of breathing (Diaz, 2002) (see Table 20).

Five within-subject crossover studies assessed ventilatory/breathing pattern parameters with bilevel NIPPV compared to different types of bilevel ventilators (Ambrosino, 1992; Highcock, 2003), other types of ventilation (Lien, 1993), LTOT (Lin, 1996), and different bilevel pressure settings (Nava, 2001). Meta-analysis on all 5 studies, for a total of 87 subjects, showed a combined statistically significant result in favour of bilevel NIPPV for increased VT (MD = 195.64, 95% CI 21.97 to 369.31; $p = 0.03$). Two of the studies (Ambrosino, 1992; Nava, 1993), with a combined total of 27 subjects that reported inspiratory time (Ti), did not show a significant increase with bilevel NIPPV (MD = 0.34, 95% CI -0.66 to 1.33) (see Figures 9 and 10). Four studies (Ambrosino, 1992; Highcock, 2003; Lien, 1993; Nava, 1993) showed an overall effect in favour of bilevel NIPPV for a significant increase in mean inspiratory flow (VT/Ti) (see Figure 11). The study by Nava, 1993, which compared different pressure level settings, showed statistically significant increases in VT/Ti on IPAP/EPAP of 10/0, 20/0, and 20/5, but not with a setting of 10/5 cmH20 with the least pressure difference (see Table 20). Three within-subject crossover studies (Ambrosino, 1992; Highcock, 2003; Nava 1993) with 43 subjects, did not favor an effect for bilevel NIPPV (MD = 0.41, CI -3.77 to 5.42) in significantly changing the respiratory duty cycle (Ti/Ttot) (see Figure 12).

Five of 7 observational COPD studies, 2 comparing bilevel NIPPV to other types of ventilation (Bianchi, 1998; Vanpee, 2002a), one study comparing to exercise (Nava, 2001), and 2 comparing to different bilevel pressure settings (Vanpee, 2002b; Vitacca, 2000), assessed VT. All 5 studies reported an increase in VT with bilevel NIPPV, 3 with a statistically significant increase (Bianchi, 1998; Vanpee, 2002a; Vitacca, 2000), while 2 studies (Nava, 2001; Vanpee, 2002b) did not reach statistical significance. VE also increased significantly in 2 studies (Vanpee, 2002a; Vitacca, 2000) and nonsignificantly in the study by Bianchi (1998). Ti/Ttot increased significantly in 2 studies (Nava, 2001; Vanpee, 2002a). The study by Bianchi (1998) also reported no change in Ti and an increase in VT/Ti that did not reach statistical significance (Table 21).

Respiratory Muscle Function/Work of Breathing. Three COPD RCTs (Casanova, 2000; Clini, 2002; Renston, 1994) reported non-statistically significant increases in maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) when comparing bilevel NIPPV and LTOT to LTOT (Casanova, 2000; Clini, 2002) and bilevel NIPPV to sham ventilation (Renston, 1994). The combined result for MIP (Clini, 2002; Renston, 1994) with 101 subjects, favoured bilevel NIPPV, although not with statistical significance (WMD = 4.45, 95% CI -4.52 to 13.43, p = 0.33) (see Figure 13). The study by Casanova (2000) reported MIP in a different unit of measure and therefore could not be combined with the other 2 studies for meta-analysis. The RCT by Renston (1994) with

17 subjects, reported a statistically significant decrease (66.6±6 %) in diaphragmatic EMG with bilevel NIPPV during exercise, consistent with respiratory muscle rest (see Table 22).

One RCT (Diaz, 2002) that assessed the effect of bilevel versus sham NIPPV on lung hyperinflation in 36 subjects with severe stable hypercapnic COPD, reported statistically significant decreases in mean inspiratory pressure swing (PI), dynamic intrinsic PEEP (PEEPidyn), dynamic lung elastase (ELdyn), inspiratory lung resistance (RL), tension time index (TTI), consistent with reduced lung hyperinflation and inspiratory mechanical workload. Associated slight and non-statistically significant increases in maximal inspiratory pressure (PImax), maximal transdiaphragmatic pressure (Pdimax), and tension time index of the respiratory muscles (TTdi) after NIPPV were also reported in this study. One RCT (Garrod, 2000) that compared bilevel NIPPV and exercise to exercise alone, showed a significant increase in PImax and nonsignificant increase in PEmax in a group of 37 subjects who were less hypercapnic (baseline $PaC0_2$ 45.6±7.79 mmHg) than the bilevel group in the study by Diaz (2002) (see Table 22).

Five out of 10 within-subject crossover studies reported parameters related to respiratory muscle function/work of breathing. The study by Ambrosino (1992) reported a decrease in EMGdi (which was not statistically significant), suggesting reduced diaphragmatic activity during bilevel NIPPV, in a group of 7 hypercapnic subjects with severe stable COPD. The study by Lien (1993) reported a statistically significant decrease in EMGst of -62.93±23.27% in 4 COPD subjects with an FEV1 < 0.55L, compared to EMGst of -32.45±42.79% in 7 subjects with an FEV1 greater than 0.55L after 40 minutes of bilevel NIPPV. This study also reported a nonsignificant decrease in

PImax, and nonsignificant increase in PEmax (see Table 23). Combined PImax and PEmax data for 2 within-subject crossover studies (Lien, 1993; Lin, 1996) however, favored a significant effect for bilevel NIPPV (MD 4.85; CI 0.25 to 9.44; $p = 0.04$) and (MD 4.82; CI 0.56 to 9.09; $p = 0.03$), respectively, favoring increased respiratory muscle strength (see Figures 14 and 15). Non-statistically significant increases MIP and MEP, also favoring slightly increased respiratory muscle strength with bilevel NIPPV, were reported in 2 within-subject crossover studies (Lin, 1996; Strumpf, 1991) that compared bilevel NIPPV and LTOT to LTOT, and bilevel NIPPV to spontaneous breathing, respectively. A statistically significant decrease in Pdi was reported by one within-subject crossover study (Nava, 1993), with all four levels of Bilevel NIPPV pressures (IPAP/EPAP of 10/0, 10/5, 20/0, 20/5 cmH_20), in 7 subjects with severe stable COPD. This study also reported a statistically significant decrease in PEEPidyn with the addition of PEEP $5cmH_20$ to nasal PSV of 10 and 20 cmH_20 (see Table 23).

There were 4 observational studies that assessed PEEPidyn as an outcome variable in response to bilevel NIPPV use. Two of the studies, one that compared bilevel and exercise to exercise alone (Nava, 2001), and one study that compared bilevel NIPPV to other types of ventilation (Vanpee, 2002a), reported nonsignificant reductions in PEEPidyn (see Table 24). One study (Vitacca, 2000) with 23 COPD subjects, that compared spontaneous breathing to patients' 'usual' and 'physiological' bilevel NIPPV settings (mean IPAP/EPAP of 16/4 and 15/3 cmH_20, respectively), showed a statistically significant reduction in PEEPidyn with both pressure level settings ($p < 0.01$). Pes, Pdi, PTPdi/b, PTPdi/min and PTPdi/VE were also significantly decreased in this study compared to spontaneous breathing, consistent with reduced diaphragmatic effort. The study by Vanpee (2002b) demonstrated a statistically significant increase in PEEPidyn, however this study compared active, resistive, and relaxed respiratory behaviors in COPD subjects while on bilevel NIPPV. The study found that PEEPidyn increased with active inspiratory behaviors while on NIPPV pressure levels of 10 cmH_20/ 0 cmH_20 ($p < 0.001$), but the increase in PEEPidyn was much less (not statistically significant) while on a pressure level of 10/5 cmH20 (Vanpee, 2002b). The study also recorded statistically significant increases in WOB/min (14.47±-9.43 to 28.55±-25.35 J/min, p = 0.008) and Wdi/min (16.13±-8.3 to 26.97±-15.83J/min, p = 0.003) while COPD subjects performed active inspiratory behaviors on PSV 10/0 cm H20. In a nonequivalent group study by Vanpee (2002a) that assessed the effects of bilevel NIPPV on inspiratory work of breathing, statistically significant reductions in both Wdi/min ($p < 0.01$) and WOB/min ($p < 0.001$) for pressure levels of 5 to 20/0 cmH_20, and also in WOB/min for pressure levels of 5 to 20/5 to 10 cmH_20 were reported in the hypercapnic group, with increasing ventilatory parameters proportionate to increasing levels of bilevel pressure support (see Table 24).

Exercise Tolerance. Four COPD RCTs assessed exercise tolerance. Three of the 4 studies used the 6MWT as a measure of exercise tolerance and when the data were combined, analysis showed no effect form the bilevel NIPPV group (see Figure 16). Two of the 3 shorter studies (Renston, 1994; Gay, 1996) that were 5 days and 3 months respectively, compared bilevel NIPPV to sham NIPPV. The third study (Clini, 2002) which was 2 years in length, compared bilevel NIPPV and LTOT to LTOT alone. The multicentric study by Clini (2002) reported a nonsignificant increase in exercise tolerance at 12 months, and a non-significant decrease at 24 months. When analysis was rerun without the longer 2 year study, bilevel NIPPV was favoured, although this was not statistically significant. The fourth trial (Garrod, 2000) demonstrated a significant increase of 100 meters ($p < 0.001$) on the shuttle walk test in the bilevel NIPPV group after 8 weeks of bilevel NIPPV (see Table 25).

Two within-subject crossover studies assessed exercise tolerance (Highcock, 2003; Meecham-Jones, 1995) and used different measures (treadmill walk test and 6MWT, respectively). Highcock (2003) reported a significant decrease in exercise tolerance with bilevel NIPPV via mouthpiece (three different types of bilevel ventilators) during treadmill exercise compared to treadmill exercise unencumbered. Meecham-Jones (1995) showed no significant change in exercise tolerance after a three month period of bilevel NIPPV and LTOT (see Table 25).

Two out of 3 observational studies reported statistically significant improvement in exercise tolerance. Bianchi (1998) reported increasingly statistically significant improvement in exercise tolerance with CPAP ($p < 0.05$) bilevel PSV ($p < 0.05$), and PAV ($p < 0.05$) modes, respectively. A second nonequivalent group repeated measures study (Clini, 1998), that compared bilevel NIPPV and LTOT to LTOT alone, reported a statistically significant increase in exercise tolerance on 6MWT at 2 and 3 years ($p < 0.01$) in 28 patients who tolerated, and chose to continue bilevel NIPPV. The third study (Nava, 2001), which compared bilevel NIPPV and exercise to exercise alone, reported a non-statistically significant increase in exercise tolerance (see Table 25).

Dyspnea. Data could not be combined for all of the RCTs that assessed dyspnea, due to the different measurement scales used. Two of the 4 COPD RCTs that assessed dyspnea as an outcome used the Borg dyspnea rating scale (Casanova, 2000; Renston, 1994). Combined data for these two studies failed to favour an effect for bilevel NIPPV toward dyspnea reduction (see Figure 17). Taken separately, however, each of the RCTs demonstrated a statistically significant improvement in dyspnea in the bilevel NIPPV treatment group. Renston (1994) showed a statistically significant 66.3% reduction in dyspnea ($p < 0.01$) in the bilevel NIPPV group, but not in the sham NIV group. There was a significant reduction in dyspnea in the study by Casanova (2000) at 3 months on two dyspnea scales ($p = 0.035$, Medical Research Council Dyspnea scale; $p = 0.039$, Borg scale). This improvement in dyspnea was maintained at 6 months on the Borg scale ($p = 0.033$) in the bilevel NIPPV and LTOT group of 20 subjects, while dyspnea in the 24 subjects in the LTOT control group remained unchanged. Another RCT by (Clini, 2002) that used the Medical Research Council Dyspnea Scale (MRCD) to assess dyspnea in a group of 47 subjects, reported a statistically significant reduction in dyspnea in the bilevel NIPPV with LTOT group at both 12 ($p = 0.048$) and 24 ($p = 0.013$) months, while dyspnea in the LTOT control group increased slightly. The dyspnea portion of the Chronic Respiratory Disease Questionnaire (CRDQ) in the fourth RCT (Garrod, 2000) in the bilevel NIPPV and exercise group of 17 subjects, showed a statistically significant improvement ($p < 0.05$) after 12 weeks, which was not found in the exercise only control group (see Table 26).

One of two nonequivalent group studies (Clini, 1998) initially showed a $23 \pm 12\%$ reduction in dyspnea at one year in the NIPPV group, which did not persist over the 3 year study interval. There was a statistically significant decrease in dyspnea for both the NIPPV and exercise group ($p < 0.005$) as well as the exercise alone group ($p < 0.05$) on the Visual Analogue Scale (VAS), in a more recent non-equivalent group 4 week study by Nava (2001) that compared bilevel NIPPV and exercise to exercise alone (see Table 26).

There were only 2 COPD within-subject studies in this systematic review that measured dyspnea. One within-subject crossover study assessed dyspnea (Strumpf, 1991). There was no change in dyspnea according to the Dyspnea Scale of Mahler in the 7 patients who completed this 6 month trial comparing bilevel NIPPV to spontaneous breathing (Strumpf, 1991). One within-subject repeated measures study (Bianchi 1998) that compared different modes of NIPPV (CPAP, BiPAP, and PAV), demonstrated a statistically significant reduction in dyspnea ($p < 0.05$) with bilevel NIPPV compared to sham NIV and CPAP. This study was a short 2 day trial in which dyspnea was measured in subjects on different modes of ventilation during exercise with a cycloergometer (see Table 26).

Sleep. There were 3 COPD RCTs that studied sleep as an outcome, however the data were not combined due to differences in sleep parameters amongst studies (sleep efficiency, sleep latency, sleep quality, total sleep time) and different units reported in these studies. The most frequently reported sleep parameter included total sleep time (TST). The study by Gay (1996) showed a nonsignificant decrease of 23.7 minutes (min) total sleep time (TST), (of which 10 min constituted a significant reduction in REM sleep) in the bilevel NIPPV group, compared to a slight but nonsignificant increase in TST in the control group. The study by Garrod (2000) also reported a nonsignificant decrease in total sleep time from 56.5% (range 29-68%) of the night to 42.9 (range 25.9-53.4%) in the bilevel NIPPV group. The study by Clini (2002), which was the longest study (2 years), showed a slight but nonsignificant improvement in sleep quality score in the bilevel NIPPV group, while there was no change in the control group (see Table 27)

Sleep efficiency (SE) and TST were the most frequently reported parameters for 4 within-subject crossover COPD studies (Krachman, 1997; Lin, 1996; Meecham-Jones, 1995; Strumpf, 1991). Two of the 4 studies (Krachman, 1997; Meecham-Jones, 1995) showed statistically significant increases in both SE ($p < 0.05$ and $p < 0.001$, respectively), and TST ($p < 0.05$ and $p < 0.05$, respectively), with bilevel NIPPV, while the other 2 studies showed nonsignificant decreases in both TST and SE. Combined data analysis for the 4 crossover studies, using the generic inverse variance, slightly favored bilevel NIPPV for increase in both SE (MD 1.94; CI -14.11 to 18.0) and TST (MD 8.52; CI -74.69 to 91.73). For 2 of the studies, mean hours of bilevel NIPPV use were reported (Meecham-Jones, 1995; Strumpf, 1991) and are similar (6.9 and 6.7 hours/night, respectively). Hours of use in the other 2 studies were not clearly reported. The bilevel NIPPV pressure levels used in the 2 studies (Krachman, 1997; Meecham-Jones, 1995) that showed improvement in SE and TST were higher (IPAP/EPAP of 22±.3/3±1 and 16-22/2-4 cm H_20, respectively), than those in the Lin (1996) and Strumpf (1991) studies (8-15/<2; and 15±1/2 cmH_20 respectively) (see Table 27).

Functional Status/ADL. Two RCTs in this systematic review assessed functional status in the COPD cohort using different measurement scales, therefore data were not combined. The study by Renston (1994) showed reduced dyspnea related functional impairment for the bilevel NIPPV versus sham NIV control group on all scales (Modified Medical Research Council Dyspnea Scale/MMRCD; Oxygen-cost diagram; and BiPAP Functional Impairment Scale), which did not reach statistical significance. The second study by Garrod (2000) compared bilevel NIPPV and exercise to exercise alone. Both groups reported a statistically significant improvement in total Chronic Respiratory Disease Scale (CRDQ) total score from 68.1±20.9 to 92.2±17.0 ($p < 0.001$) and 73.3±22.4 to 85.1±23.9 ($p = 0.003$), respectively, however there was a greater improvement for all components of the scale (dyspnea, mastery, emotion, fatigue), as well as the total score for the bilevel NIPPV with exercise group (Garrod, 2000) (see Table 28).

*Health-Related Quality of Life.*Two RCTs (Clini, 2002; Garrod, 2000) reported HRQOL as an outcome, using different measurement scales. The study by Clini (2002) used 2 scales: the Saint George's Respiratory Questionnaire (SGRQ) and the Maugeri Foundation Respiratory Failure Questionnaire (MRF-28). The SGRQ showed some improvement (symptoms, activity, and impact scores) in both the bilevel NIPPV with LTOT (-5%) and LTOT control groups (-4%), but did not reach statistical significance. The MRF-28 score (cognitive behavior, activity, disability, and other components) on the other hand, showed statistically significant improvement from baseline in the bilevel NIPPV with LTOT group, compared to the LTOT only group ($p = 0.041$; 95% CI 0.13 to 4.07) at 24 months. As previously mentioned, both the NIPPV with exercise and the exercise only groups in the study by Garrod (2000) showed statistically significant improvement in CRDQ total scores. The difference in change scores between the groups for both the CRDQ total score (difference of 12.3, $p = 0.03$) and the fatigue component (difference of 3.41, $p = 0.01$), supported a significantly greater improvement in the bilevel NIPPV and exercise group compared to the exercise only group (Garrod, 2000) (see Table 29).

Only one COPD within-subject study (Meecham-Jones, 1995) reported HRQOL as an outcome measure. SGRQ scores in this study, which compared baseline measurements obtained during the 4 week run-in period with patients on "normal therapy", to those obtained after a 3 month trial of LTOT, and a 3 month trial of bilevel NIPPV, showed significantly improved HRQOL (total score, $p = 0.001$; impact score, $p = 0.002$; symptom score, $p = 0.007$) (see Table 29).

Morbidity. There were 3 COPD studies in this systematic review that measured morbidity in terms of hospital and ICU admissions. Two of the 3 studies were RCTs (Casanova, 2000; Clini, 2002), and the remaining study was a nonequivalent group study (Clini, 1998). All 3 studies compared bilevel NIPPV and LTOT to LTOT alone. Hospital and ICU admission rates between both the treatment and control groups in the two RCTs showed a non-statistically significant difference (see Table 30). The data was not combined due to the different unit of measure used in both studies. Taken separately, the bilevel NIPPV group in each of these 2 studies had a substantial reduction in total hospital admissions compared to baseline. The Casanova (2000) study reported a 10% decrease in total hospital admissions ($p < 0.05$) at 3 months in the bilevel NIPPV group, which did not persist at 6 or 12 months. Although the Clini (2002) study reported a 45% decrease in total hospital admissions compared to a 3 year period leading up to the study, this was not statistically significant. The control group in this 2 year study actually had an increase in total hospital admissions by 27%. There was a 1% versus 3% endotracheal intubation/ICU admission rate in the NIPPV versus LTOT group in the study by Casanova (2000), whereas the study by Clini (2002) showed a 75% reduction in the bilevel NIPPV group compared to a 20% increase in the LTOT control group (see Table 30).

The nonequivalent groups study by Clini (1998) showed a statistically significant reduction in hospitalization (days/pt/year) in both the NIPPV and LTOT groups, with a greater reduction in the NIPPV versus LTOT group ($p < 0.001$). ICU admissions in this study significantly decreased in the NIPPV group only, from 1.0±0.7 to 0.2±0.3 days/pt/year, compared to 1.2±0.4 to 0.9±0.3 days/pt/year in the LTOT group ($p < 0.0001$) (see Table 30). The need for endotracheal intubation in this study was also significantly less in the NIPPV group (0.10±0.10 intubations/pt/year) than in the LTOT group (0.50±0.3 intubations/pt/year) ($p < 0.05$).

Mortality. Mortality rate was reported in 2 RCTs and 1 non-equivalent group study (Casanova, 2000; Clini, 2002; Clini, 1998). In all 3 COPD studies there was no significant difference between the bilevel NIPPV group with LTOT group compared to the LTOT only group (see Table 31). The mortality rate in the 1 year study by Casanova (2000) was the highest (78% in both groups), whereas the 2 year study by Clini (2002) reported mortality rates of 18% and 17% for the NIPPV and LTOT groups, respectively. The longest study (Clini, 1998) reported mortality rates of 16%, 33%, and 46% for the bilevel NIPPV and LTOT group, and 13%, 28%, and 50% for the LTOT only group at 1, 2, and 3 years, respectively (see Table 31).

Comfort/Compliance. Fourteen out of 22 COPD studies described comfort/compliance issues related to bilevel NIPPV use (5 RCTs and 9 observational studies), while subjects in the remaining 8 COPD studies tolerated bilevel NIPPV (see Table 32). Information regarding comfort/compliance issues was based on patient and/or family reporting, combined with equipment monitored use of bilevel NIPPV (i.e. ventilator time counters). The bilevel NIPPV trial period in all 8 COPD studies that did not have compliance issues, was 3 weeks or less. Five of the 14 COPD studies that did report comfort/compliance issues had a bilevel NIPPV trial period of less than 1 week, and the remaining 9 COPD studies had a bilevel NIPPV trial period of 1 month to 3 years. The most prevalent complaints were related to asynchrony (Ambrosino, 1992; Ambrosino, 1993; Lin, 1996; Vanpee, 2002b) and sleep (Garrod, 2000; Gay, 1996; Renston, 1994; Strumpf, 1991). Inability to tolerate pressure-level settings (Ambrosino, 1993; Casanova, 2000; Nava, 1993), dry nose and/or mouth (Garrod, 2000; Clini, 1998; Strumpf, 1991), or mask/interface intolerance due to problems such as leak or nasal skin lesions/skin breakdown (Clini, 1998; Gay, 1996; Lin, 1996; Nava, 2001) were also reported. Two studies reported bilevel NIPPV intolerance with no reason cited. One study that reported inability to sleep, cited ventilator noise as one of the reasons. Seven of the 8 studies that did not report comfort/compliance issues related to bilevel NIPPV included NIPPV trials of < 1 week. The remaining study had an NIPPV trial length of 3 weeks (see Table 32).

Restrictive Studies

There were 8 restrictive bilevel NIPPV studies in this systematic review, which were all within-subject designs, consisting of 3 crossover and 3 non-crossover studies. Comparisons included bilevel NIPPV versus spontaneous breathing; bilevel NIPPV with exercise versus exercise alone; and different types of bilevel NIPPV ventilators (see Table 13).

Gas Exchange. Six restrictive studies that compared bilevel NIPPV to spontaneous breathing reported on gas exchange as an outcome. PaO_2 was improved in all studies, with the greatest rise in mean PaO_2 in the studies by Waldhorn (1992) (increase of 14.6 mmHg, SE 16.99839) and the case study by Strumpf (1990) (increase of 23mmHg, SE 11.64044). The remaining 4 studies demonstrated smaller improvements in mean PaO_2 with increases of 7.75, 3.7, 5.0, and 6.9 mmHg, respectively (Ergun, 2002; Fanfulla, 1997; Hill, 1992; Nauffal, 1996). A seventh study did not show improvement in SaO_2 on exercise during mouthpiece bilevel NIPPV (Highcock, 2002b). The eighth study (Highcock, 2002a) that compared 2 different bilevel NIPPV ventilators (Quantum PSV and Sullivan VPAP II ST) found no significant difference in mean nocturnal SaO_2 between the 2 ventilators (see Table 33).

Four out of 5 restrictive studies in this systematic review that assessed nocturnal oxygenation, showed resolution of recurring desaturation on Sa02 monitoring with bilevel NIPPV. One 3 year within-subject repeated measures study (Nauffal, 1996) showed significant improvement in nocturnal O_2 saturation at 3, 6, 9, 12, and 18 months in patients with kyphoscoliosis and neuromuscular disorders ($p < 0.05$). In another study (Hill, 1992), there was statistically significant deterioration in nocturnal oxygenation ($p < 0.05$) after bilevel NIPPV was withheld for 1 to 2 weeks in a group of patients with restrictive pulmonary disease. The remaining 2 studies (Fanfulla, 1997; Waldhorn, 1992) showed improvement in nocturnal SaO_2, but was not statistically significant (see Table 33).

Statistically significant improvement in daytime $PaCO_2$ was demonstrated in 2 out of 6 restrictive studies (Ergun, 2002; Nauffal, 1996). The significant improvement in

$PaCO_2$ in the study by Nauffal (1996), which included 2 groups of subjects with CRF due to restrictive pulmonary disease, occurred in the kyphoscoliosis group, but not in the neuromuscular disease (NMD) group. The case study of 4 subjects by Strumpf (1990) also showed substantial reduction in $PaCO_2$ (-19 mmHg). Of the 3 remaining studies, one study (Fanfulla, 1997) that consisted of a 2 year trial of bilevel NIPPV, had a slightly increased (1.2 mmHg) $PaCO_2$ at 2 years, with a significant negative correlation between vital capacity (VC) and $PaCO_2$ ($r= -0.89$, $p < 0.01$) in subjects whose VC had a significant and progressive decline ($p < 0.001$) during the study period. Another study (Hill, 1992) did not show a significant change in daytime $PaCO_2$ in a group of subjects who had previously been using nocturnal noninvasive ventilation, after withdrawal (increase of 2.0 mmHg off NIPPV), and following resumption of bilevel NIPPV (decrease of 2 mmHg). The study by Waldhorn (1992) showed a substantial improvement in daytime $PaCO_2$ (-16 mmHg).

Bilevel NIPPV demonstrated statistically significant improvement in nocturnal $PaCO_2$ in 1 out of 3 studies (Waldhorn, 1992). Significant worsening of hypercapnia was evident in 1 of 2 studies that measured nocturnal $PtCO_2$ (Hill, 1996) after a period off nocturnal bilevel NIPPV. There was very little difference in nocturnal $PtCO_2$ in the study by Highcock (2002a), which compared 2 different bilevel ventilators (see Table 33).

Lung Function. For the purposes of this systematic review, lung function outcomes for the restrictive pulmonary studies will include VC and forced vital capacity (FVC). In 1 out of 5 restrictive studies (Ergun, 2002) there was a statistically significant improvement in FVC (from 35 to 50% predicted, $p < 0.01$) after a 15 day trial of bilevel NIPPV at 2 hours/day. The remaining studies did not show significant improvement in

VC or FVC. In the longest study (Fanfulla, 1997), there was a slower than usual decline in FVC over 2 years. In a within-subject repeated measures study by Nauffal (1996), FVC increased slightly by 2.8% at 18 months. Withdrawal of bilevel NIPPV for a short period of time (1 to 2 weeks) in another study (Hill, 1992) showed no significant change in FVC (decrease of 18±19 mls). The study by Waldhorn (1992) showed no significant change in FVC after a 3 month trial of bilevel NIPPV (see Table 34).

Ventilatory/Breathing Pattern. Two restrictive studies (Highcock, 2002b; Strumpf, 1990) in this systematic review assessed ventilatory/breathing pattern. In one study (Strumpf, 1990), which compared spontaneous breathing and the subjects' standard non-bilevel nocturnal NIPPV assistance to bilevel NIPPV, the latter showed an increase in mean values of VE (1.625 L/min) and VT (93.75 mls) beyond VE and VT with standard ventilation. The second study (Highcock, 2002b), that assessed ventilation during exercise, compared 3 different bilevel ventilators via mouthpiece and found significant increases in VT ($p = 0.02$) and VT/Ti ($p = 0.04$) during the ventilator walks, as well as slight but nonsignificantly increased Ti/Ttot ratio (see Table 21). Walking distance was significantly lower with the bilevel NIPPV walks versus the unencumbered walking.

Respiratory Muscle Function/Work of Breathing. The study by Ergun (2002), which measured EMGdi to assess the effectiveness of bilevel NIPPV in reducing the work of inspiratory muscles, reported a nonsignificant decrease in 4 out of 12 subjects for before and after values following a 15 day NIPPV trial period consisting of 2 hrs/day NIPPV use. Naufal (1996) assessed mean inspiratory pressure (MIP) as a measure of respiratory muscle endurance and found a slight improvement, which persisted at 18 months in the kyphoscoliosis group, but did not reach statistical significance. MIP in the NMD group in the same study did not follow the same trend, with a slight reduction at 18 months. There was a nonsignificant increase in maximal inspiratory mouth pressure (PImax increase of -1 cmH20) and nonsignificant decrease in maximal expiratory mouth pressure (PEmax decrease of 2 cmH$_2$0) in the study by Hill (1992), which assessed for respiratory muscle fatigue after withdrawal of bilevel NIPPV for a period of 8 ± 2 days in 4 subjects with restrictive chest wall disease, and 2 patients with muscular dystrophies (see Table 35).

Exercise Tolerance. One out of 2 restrictive studies (Ergun, 2002) that assessed exercise tolerance showed significant improvement in the distance walked during the 6 minute walk test after 15 days of daytime bilevel NIPPV for 2 hours/day ($p < 0.05$). The second study (Highcock, 2002b), that used repeated measures to assess exercise tolerance with the use of 3 different bilevel NIPPV ventilators via mouthpiece, showed a statistically significant decrease in treadmill walking distance for all the ventilators compared to unencumbered treadmill walking ($p = 0.048$) (see Table 36).

SymptomRelief. Three studies assessed symptom relief related to bilevel NIPPV use in restrictive pulmonary disease. One study (Hill, 1992) used a VAS for symptom scoring, and reported significantly reduced energy, increased morning headaches (from 0.3 ± 0.2 to 4.8 ± 1.1, $p < 0.05$) and feeling rested on fewer mornings (from 6.5 ± 0.5 to 4.8 ± 1.1, $p < 0.05$) after being off bilevel NIPPV for 8 ± 2 days, which subsequently improved once NIPPV was reinitiated. Of the remaining 2 studies, both relied on patient self report (Waldhorn, 1992; Fanfulla, 1992). Both studies found that subjects had reduced daytime somnolence, and all subjects in 1 of the 2 studies (Fanfulla, 1997) reported the resolution of their daytime symptoms of sleep disordered breathing, including morning headache, diurnal fatigue, and loss of concentration, following initiation of bilevel NIPPV (see Table 39).

Dyspnea. Three of 4 restrictive studies (Ergun, 2002; Hill, 1992; Nauffal, 1996) reported statistically significant improvement in dyspnea with bilevel NIPPV use. ATS score decreased significantly ($p<0.01$) in one study (Ergun, 2002) from 2.5±0.9 to 1.6±0.4 after 15 days of NIPPV at 2 hours/day. Another study (Hill, 1992) showed significantly worsened dyspnea with a VAS score increase from 3.1±1.46 to 5.0±1.95 ($p < 0.05$) after withdrawal of NIPPV for 8±2 days, which subsequently improved with re-initiation of bilevel NIPPV to VAS score of 2.7±0.5. A third study (Nauffal, 1996) reported significant dyspnea reduction at 6 months in a group of 35 subjects with kyphoscoliosis (effect size = 1.30; $p < 0.05$), with sustained improvement in the follow-up to 18 months. There was no dyspnea reduction in the NMD group in the Nauffal (1996) study however. One study (Waldhorn, 1992) that used patient reporting rather than a validated scale to measure dyspnea, reported reduced daytime dyspnea after 3 months of bilevel NIPPV (see Table 37).

Sleep. Two out of 8 restrictive studies in this systematic review assessed sleep. One of the 2 studies (Hill, 1992) found sleepiness score significantly increased (from 2.0±0.5 to 3.9±0.8 , $p < 0.05$) and reduced sleep time (from 7.2±0.04 to 5.6±0.8, $p < 0.05$) after bilevel NIPPV was held for 8±2 days. The second study (Highcock, 2002a), that compared 2 types of bilevel NIPPV ventilators, reported no significant differences in total sleep time, sleep latency, or sleep efficiency between the Quantum or Sullivan VPAP ventilators (see Table 38).

Functional Status/ADL and HRQOL. None of the 8 restrictive studies in this systematic review used a functional assessment/ADL validated scale to assess functional status. Only one study assessed HRQOL using the SF-36 questionnaire (Nauffal, 1996), and found improvements in every category of the instrument in the kyphoscoliosis group, with statistically significant increases persisting at 18 months for social functioning, emotional and physical roles ($p < 0.05$). In the NMD group in the same study, significant improvement in the physical functioning category was sustained at 18 months ($p < 0.05$) (see Table 29).

Morbidity and Mortality. Only one out of 8 restrictive studies (Nauffal, 1996) assessed morbidity, and found significantly reduced hospitalization rates in both the kyphoscoliosis group (from 1.2 ± 1.8 to 0.8 ± 1.20, $p = 0.01$) and the NMD group (from 1.1 ± 1.2 to 0.3 ± 1.2, $p = 0.005$) (see Table 30). None of the restrictive studies in this systematic review assessed mortality.

Comfort/Compliance. Two out of 8 restrictive studies in this systematic review (Hill, 1992; Waldhorn, 1992) reported that all patients tolerated bilevel NIPPV well. The remaining 6 studies do not discuss tolerance or comfort/compliance issues (Ergun, 2002; Fanfulla, 1997; Highcock, 2002a; Highcock, 2002b; Nauffal, 2002; Strumpf, 1990).

Mixed Studies

There were 2 mixed studies (with COPD and restrictive pulmonary disease cohorts) in this systematic review that assessed effectiveness of different bilevel NIPPV pressure levels (Elliott, 1995), and different bilevel NIPPV modes (Restrick, 1993), in the management of nocturnal hypoventilation. Outcome measures common to both included gas exchange (SaO_2, $PtCO_2$), and assessment of sleep.

Gas Exchange. In the 3 night study by Restrick (1993), the mean daytime $Pa0_2$ reported for the combined study group (both COPD and restrictive subjects) showed a significant improvement for both the S mode (increase from 7.9kPa/59.25 mmHg to 8.9kPa/66.75mmHg; CI for the difference of 1.0/7.5mmHg = 0.1 to 0.9, p = 0.039) and ST bilevel NIPPV mode (increase from 7.9kPa/59.25mmHg to 9.1kPa/68.25mmHg; CI for the difference of 1.2 = 0.8 to 1.7, p = 0.0001). Mean daytime $PaC0_2$ on the S mode, compared to the non-ventilation control measures, showed significant improvement (decrease from 7.26kPa/54.45mmHg to 7.00kPa/52.5mmHg; CI for the difference of -0.26kPa/1.95mmHg = -0.49 to -0.02, p = 0.034). The decrease in daytime $PaC0_2$ on the ST mode, however, did not reach significance (from 7.30kPa/54.75mmHg to 7.16kPa/53.7mmHg; CI for the difference of – 0.14kPa/1.27mmHg = – 0.51 to – 0.20, p = 0.36). Nocturnal studies showed a statistically significant increase in $Sa0_2$ in the combined group on both the S mode (p = 0.0012) and the ST mode (p = 0.0007). Mean nocturnal $PtC0_2$ decreased significantly on the S mode (p = 0.01) but not on the ST mode (p = 0.08). When individual data reported in the study is taken separately according to group, mean nocturnal $Sa0_2$ increased from 86.3±8.14% on air, to 89.92±4.5% and 89.86±5.84% on S and ST modes respectively in the COPD group; and from 88.1±4.8% on air, to 93.13±2.5% and 92.64±2.79% on S and ST modes in the restrictive group. Nocturnal $PtC0_2$ decreased significantly in the combined group on the S mode (decrease of -0.4kPa/3.0mmHg, p = 0.01), and nonsignificantly (decrease of -0.2kPa/1.5mmHg, p = 0.08) on the ST mode. The mean nocturnal $PtC0_2$ according to separate data for the COPD group, decreased from 61.35±12.62 mmHg on air, to 58.5±12.12 and 58.65±9.2

mmHg on S and ST modes, respectively; and from 54.32±3.92 mmHg on air, to 51.21±4.85 and 53.03±4.78 mmHg on S and ST modes, respectively in the restrictive group. There were no statistically significant differences for Pa0$_2$, PaC0$_2$, mean nocturnal Sa0$_2$, or PtC0$_2$ between the COPD and restrictive groups (Restrick, 1993) (see Table 40).

In the second study (Elliott, 1995), the COPD and restrictive groups were assessed separately, and IPAP was compared to IPAP/EPEP, with no comparison to baseline values. There were no significant improvements in mean nocturnal Sa0$_2$ or PtC0$_2$ in the COPD group with the addition of EPAP NIPPV, during any sleep stage. Minimum nocturnal Sa0$_2$ 77.1±6.7% and PtC0$_2$max of 8.1±1.4 kPa/60.75±10.5 mmHg on IPAP, improved significantly in the restrictive group with the addition of EPAP, resulting in Sa0$_2$ of 83.6±4.20% (p = 0.02), and PtC0$_2$ of 7.3±0.9 kPa (54.75±6.75 mmHg, p = 0.04). In the NMD group however, with the addition of EPAP, there were significant improvements in nocturnal minimum Sa0$_2$ levels during wakefulness (77.1±6.7% with IPAP; 83.6±4.2% with IPAP/EPAP, p = 0.02), and during NREM sleep (77.1±6.7% with IPAP; 85.4±5.0% with IPAP/EPAP, p = 0.02), but not during REM sleep. Maximum PtC0$_2$ in the NMD group was also significantly lower during wakefulness (7.9±1.2 kPa with IPAP; 7.3±0.9 with IPAP/EPAP, p = 0.04), but not during REM or NREM sleep (see Table 25).

Sleep. In the study by Restrick (1993), no statistically significant difference was found between the control, bilevel S, or ST mode nights on the VAS scores that assessed comfort and quality of sleep. The VAS score response to how well subjects slept (from 4.8 on air, to 1.3 on S mode and 2.1 on ST mode), showed the greatest improvement with the S mode (lower score reflecting improvement). In the study by Elliott (1995), that found no significant difference in the mean nocturnal Sa0$_2$ and PtC02 values between IPAP and IPAP/EPAP during any sleep stage for the NMD or COPD group, deterioration in sleep quality was noted during the IPAP/EPAP night in the NMD group during NREM (sleep time decreased from 266±44 minutes/4.43±0.73 hours to 226±32 minutes/3.76±0.53 hours, $p = 0.05$) and stage 2 sleep (203±43 minutes/3.38±0.71 hours to 158±47 minutes/2.63±0.78 hours, $p = 0.04$). Total sleep time in this group, although reduced, did not reach statistical significance (from 321±43 minutes/5.35±0.71 hours to 280±73 minutes/4.6±1.21 hours, $p = 0.15$). Total sleep time in the COPD group increased (from 229±123 minutes/3.81±2.05 hours to 254±75 minutes/4.23±1.25 hours, $p = 1.0$) but not significantly (see Table 38).

Chapter Four

Discussion of Findings

The purpose of this systematic literature review was to critically appraise and summarize existing studies involving the nature and extent of effectiveness of bilevel NIPPV in the management of the morbidity associated with chronic respiratory failure in COPD and restrictive pulmonary disorders. This review included both randomized controlled trials (RCTs) and observational studies. There were 22 COPD cohort studies; 6 RCTs and 15 observational (9 crossover and 7 noncrossover) studies. The restrictive pulmonary cohort studies consisted of 8 noncrossover observational studies.

Effectiveness of Bilevel NIPPV in the COPD Cohort

Respiratory Function

Combined analysis of the within-subject crossover studies supported a significant improvement in gas exchange (both PaO_2 and $PaCO_2$) with bilevel NIPPV, while combined analysis of the RCTs did not. Using patients as their own controls would assist in controlling for differences in disease severity, as it is likely that in severe advanced COPD, smaller differences in lung function between subjects may account for failure of existing trials to consistently demonstrate significant improvement in gas exchange with bilevel NIPPV. Additionally, the study by Nava (2001) found that the extent of improvement in gas exchange correlated with disease severity (greater response in COPD subjects with greater disease severity), which suggests a subset of responders to bilevel NIPPV.

Other issues related to the effectiveness of bilevel NIPPV in improvement of gas exchange for the COPD cohort in this systematic review include; hours of use, bilevel pressure levels, and choice of outcome measurement. The variability among the studies with respect to these issues likely contributes to some of the confusion in determining effectiveness of bilevel NIPPV use in severe stable COPD. Reduction of hypercapnia within the RCTs was greater in the 4 RCTs that had higher hours of bilevel NIPPV use (Casanova, 2000; Clini, 2002; Diaz, 2002; Garrod, 2000) than in the remaining 2 studies.

Within the crossover studies, those which used lower bilevel pressures (Lien 1993; Lin 1996) showed the least improvement in $PaC0_2$ reduction, than the remaining crossover studies that reported greater improvement in $PaC0_2$ reduction (Ambrosino, 1992; Krachman, 1997; Marangoni, 1997; Meecham-Jones, 1995; Nava, 1993) Improvements in ventilatory parameters and reduction of PEEPidyn reported in 2 COPD studies, were proportional to the bilevel NIPPV pressures applied (Nava, 1993; Vanpee, 2002a). One of these studies (Vanpee 2002a) included ABGs as an outcome measure, and showed the greatest improvement in $PaC0_2$ on higher pressure levels of 20/5 cmH20, similar to the study by Ambrosino (1993).

Nocturnal $PtC0_2$ monitoring may be a more dynamic measure of effectiveness of bilevel NIPPV in reduction of hypercapnia in subjects with severe COPD than arterial blood gases (ABGs) alone. Consistent reduction of hypercapnia was noted on continuous nocturnal monitoring of $PETC0_2$ and $PtC0_2$ in the Strumpf (1991) and Meecham-Jones (1995) studies, that did not show the same extent of improvement in daytime $PaC0_2$. The extent of reduced hypercapnia, which was greater in the Meecham-Jones (1995) study, may also suggest that the effectiveness of bilevel NIPPV and degree of the response is greater in COPD subjects with a higher baseline PaC02.

The 10 COPD studies in this systematic review that reported lung function as an outcome did not show significant improvement for the COPD group in response to bilevel NIPPV. Although there was no significant improvement in lung function, at the same time there was no significant deterioration in this elderly hypercapnic cohort with severe advanced lung disease. The longest COPD study of 3 years (Clini, 1998), had less of a reduction in FEV1 in the bilevel NIPPV group compared to the non-NIPPV group over the 3 year study, which may support a preventative and/or supportive role for bilevel NIPPV in COPD. One study in this review reported a reduction in %RV/TLC at one year (Casanova, 2000), suggesting reduced hyperinflation, although not statistically significant, was associated with significant dyspnea reduction. Few of the remaining COPD studies reported lung function parameters that would allow a more comprehensive determination of the degree of hyperinflation for the subjects within the COPD cohort.

Although bilevel NIPPV use did not demonstrate improvement in FEV1, a number of the studies that demonstrated significant improvements in gas exchange reported concurrent statistically significant improvement in one or more outcomes related to ventilatory/breathing pattern (Ambrosino, 1992; Bianchi, 1998; Diaz, 2002; Vitacca, 2000) and/or respiratory muscle function/WOB (Diaz, 2002; Vitacca, 2000; Nava, 2001). Statistically significant improvements in some of the flow and volume indices (VE, VT, Ttot, VT/TI) in studies that assessed ventilation/breathing pattern were reported with bilevel NIPPV use (Ambrosino, 1992; Bianchi, 1998; Diaz, 2002; Highcock, 2003; Lien, 1993; Nava, 1993, Vanpee 2002a; Vitacca, 2000). Two of the daytime studies (Nava, 1993; Diaz, 2002) found that the extent of the increase in VT was greater with higher bilevel pressures (IPAP/EPAP pressure difference of at least 15cmH20), suggesting that the degree of improvement in alveolar ventilation with bilevel NIPPV in the COPD cohort may be related to the IPAP/EPAP pressure difference. These studies, as well as the study by Lin (1996), which was nocturnal and showed less reduction in VT and VE during sleep with NIPPV despite the use of lower pressures of 8 to 15/<2 cmH20, suggest a supportive role for bilevel NIPPV use in the management of CRF.

Significant reductions in VE and/or end-expiratory lung volume (PEEPidyn) consistent with reduced lung hyperinflation in response to bilevel NIPPV use, were also associated with significant improvements in gas exchange (Diaz, 2002; Nava, 1993; Nava 2001; Vanpee, 2002a; Vitacca, 2000). This suggests that increased alveolar ventilation, resulting in reduced end-expiratory lung volumes and reduced lung hyperinflation in response to bilevel NIPPV use in some individuals with severe stable COPD, may contribute to significant improvement in gas exchange. It may be possible then, that subjects with more hyperinflation may constitute a subset of subjects that respond more favorably to bilevel NIPPV, and if so, may explain some of the inconsistent findings regarding effectiveness of bilevel NIPPV in severe stable COPD.

The COPD studies that included an assessment of respiratory muscle fuction/WOB failed to consistently demonstrate significant improvements in indices related to respiratory muscle strength in response to bilevel NIPPV use. Assessment of diaphragmatic muscle activity and WOB on the other hand, (Garrod, 2000/EMG; Nava, 1993/Pdi; Nava, 2001/PTPdi/Vt ratio), demonstrated significant reductions in indices related to diaphragmatic activity/WOB favoring effectiveness of bilevel NIPPV for respiratory muscle rest associated with reduced work of breathing. One of these studies (Nava, 1993) also showed a proportionately greater reduction in diaphragmatic WOB indices with increasing IPAP, to a maximum of 20 cmH20, following the addition of 5 cmH_2O EPAP, suggesting greater respiratory muscle rest and reduction of workload proportional to bilevel NIPPV pressures used. The study by Lien (1993) showed a statistically significant reduction of respiratory accessory muscle work (EMGst) of breathing during bilevel NIPPV use, that was greater in those COPD subjects with an FEV1 less than 0.55L, versus those with an FEV1 greater than 0.55L, which may lend support for a subset of responders who may benefit from bilevel NIPPV to reduce WOB.

The study by Vanpee (2002b) that assessed respiratory behaviors (active, resistive, relaxed) while on bilevel NIPPV, suggested the possibility that some COPD patients who actively assist inspiratory behavior while on bilevel NIPPV, may contribute to increased diaphragmatic workload and metabolic demand, which in turn increases air trapping and lung hyperinflation (Vanpee, 2002b). Some patients with severe COPD are unable to tolerate bilevel NIPPV due to patient/ventilator asynchronous behavior where the patient is not allowing the ventilator to assist their spontaneous breathing due to difficulty coordinating his/her breathing efforts with the ventilator (Meyer, 1994). Severe stable COPD patients who are able to tolerate, and demonstrate some outcome improvement with bilevel NIPPV, may be those that are capable of a relaxed respiratory behavior pattern during bilevel NIPPV. The active and resistive behaviors, which may represent patient/ventilator asynchrony, might explain the reduced effectiveness of bilevel NIPPV in certain subjects who are unable to tolerate bilevel NIPPV.

Health-Related Outcomes

A number of studies reported statistically significant improvement in exercise tolerance following regular bilevel NIPPV use, including the longer study of 3 years by

Clini (1998), suggesting that periods of regular bilevel NIPPV use, during which the inspiratory mechanical load is relieved allowing respiratory muscle rest, may contribute to improvement in exercise. Exercise tolerance in the longer Clini (1998) study at 3 years had decreased from the 2 year point, which would not be surprising, given the progressive irreversible nature of severe COPD. One of the studies (Garrod, 2000) found that bilevel NIPPV, when combined with an exercise program, improved oxygenation and HRQOL in conjunction with exercise tolerance, suggesting the possibility of a supportive/adjunctive role for bilevel NIPPV in enhancing the effects of pulmonary rehabilitation. Bilevel NIPPV use during exercise did not improve exercise tolerance. Because bilevel NIPPV delivers preset IPAP/EPAP pressure levels, it may not be as responsive as other modes of NIPPV to sudden changes/increased mechanical load, ventilatory and metabolic demand that occurs during exercise. This may explain the findings in 1 COPD study that assessed exercise tolerance during bilevel NIPPV via mouthpiece (Highcock, 2003), which showed reduced exercise tolerance on all 3 types of bilevel NIPPV. Newer NIPPV modes such as proportional assist ventilation (PAV), that deliver flow and volume in proportion to each inspiratory effort, might allow more synchrony than bilevel NIPPV during NIPPV and active exercise. One study (Bianchi, 1998) that assessed exercise tolerance during NIPPV, demonstrated the greatest improvement with PAV versus sham, CPAP, and bilevel PSV.

Symptom relief was significantly improved with bilevel NIPPV use in 2 COPD studies that formally reported it as part of the HRQOL outcome. Statistically significant reduction of dyspnea associated with bilevel NIPPV use was consistently reported in both the RCTs (Casanova, 2000; Clini, 2002; Garrod, 2000; Renston, 1994) as well as the observational studies (Bianchi, 1998; Nava, 2001), which were up to 2 years in length, which is suggestive of an added benefit of bilevel NIPPV related to a supportive role in the management of chronic dyspnea in severe, advanced COPD. Generous reductions in dyspnea in the longest 3 year trial by Clini (1998) at 1 and 2 years, which were not maintained at 3 years, may be related to the severe advanced nature and further progression of COPD in this elderly cohort. McConnell and Romer (2004) recently described how the impairment of contractile properties of the respiratory muscles with resultant functional weakening and fatigue brought about by dynamic hyperinflation in COPD creates worsening dyspnea intensity, and the role of respiratory muscle training in reducing the intensity of dyspnea through improvement of the contractile properties of the respiratory muscles. It may be possible that nocturnal bilevel NIPPV, which reduces those factors that have the potential to increase dyspnea (by improving alveolar ventilation and reducing hyperinflation and addressing the factors that impair the contractile properties of the respiratory muscles), and an exercise rehabilitation program, which augments those factors that have the potential to decrease dyspnea (by addressing factors that improve contractile properties, through respiratory muscle training), are more effective in combination due to an additive effect.

Bilevel NIPPV use did not consistently improve sleep indices (TST and/or sleep efficiency) in the COPD cohort. Despite a slight reduction in sleep indices in this group during nocturnal bilevel NIPPV, the benefit of other significantly improved outcomes (gas exchange, dyspnea, symptom relief, exercise tolerance, fatigue, emotion, emotion, and/or functional status) associated with nocturnal bilevel NIPPV use may outweigh the nonsignificant reductions in sleep parameters in patients with severe COPD.

Of the 2 COPD studies that assessed functional status/ADL, the short RCT (Renston, 1994) showed a nonsignificant improvement in functional status on 3 different scales, while the longer 8 week RCT (Garrod, 2000) reported statistically significant improvement in both the treatment and control groups (greater in bilevel NIPPV with exercise group) on the LCADL assessment scale that was associated with significantly greater improvement in the 4 components of the CRDQ scale, including dyspnea and fatigue. The exercise program in the Garrod (2000) study likely contributed to improved functional status/ADL, however further improvement with the addition of bilevel NIPPV supports an additional improvement related to bilevel NIPPV.

Very few studies in this systematic review assessed health-related quality of life (HRQOL). However, only 7 of the total 23 COPD studies in this systematic review were 3 months or longer, a length that might be reasonable for HRQOL outcomes. The COPD studies that did assess HRQOL were 12 weeks to 2 years in duration, (Clini, 2002; Meecham-Jones, 1995; Garrod, 2000). All 3 studies showed statistically significant improvement in HRQOL on at least one validated HRQOL measurement scale, which may suggest a supportive role for bilevel NIPPV in rendering disease related morbidity more manageable for patients with chronic respiratory failure and reduced respiratory reserve due to COPD. The statistically significant improvement in HRQOL according to the total Chronic Respiratory Disease Questionnaire (CRDQ) and fatigue component scores for both of the groups in the Garrod (2000) study, that assessed the addition of bilevel NIPPV to an exercise program, is suggestive of a supportive, adjunctive role for bilevel NIPPV in the management of CRF in severe stable COPD. The greater improvement in fatigue in the bilevel NIPPV group might support the concept of improved alveolar ventilation, reduced mechanical load and respiratory muscle rest, with the 8 hours nocturnal ventilation used by the subjects who completed the study (Garrod, 2000). Significant improvements in HRQOL total scores in both Garrod (2000) and Meecham-Jones (1995) studies were reported to be largely due to significant improvements in the symptom component portion of the scores, which may suggest a supportive role for bilevel NIPPV in the setting of stable severe COPD.

Few COPD studies in this systematic review (Casanova, 2000; Clini, 2002; Clini, 1998) reported morbidity as an outcome, despite the significant expenditure of health care dollars devoted to treatment of COPD exacerbations. The 3 COPD studies (Casanova, 2000; Clini, 2002; Clini, 1998) that assessed morbidity were longer studies (1, 2, and 3 years, respectively). Although reductions in hospital admissions between the bilevel NIPPV and LTOT groups in the 2 RCTs (Casanova, 2000; Clini, 2002) failed to reach statistical significance, reductions in both hospital stay and dyspnea, which were associated with reduced frequency of hospital admissions within the bilevel NIPPV groups in these studies, suggests a possible preventative role for bilevel NIPPV related to management and/or reduction of morbidity in patients with CRF due to severe advanced COPD. This is further supported by significant reduction of dyspnea reported at 1 and 2 years in the study by Clini (1998), which were associated with significant reductions in frequency and duration of hospitalization, and the need for endotracheal intubation in the bilevel NIPPV group in the study by Clini (1998). Reduction of duration of hospital stay and reduced need for intubation and ICU support with bilevel NIPPV use would translate to reduced health care expenditures, as has already been demonstrated in the setting of acute respiratory failure due to COPD exacerbation (Lightowler, Jadwicha, Elliott, &

Ram, 2003). Because of the irreversible and progressive nature of COPD, it is not surprising that studies to date, including those in this review (Casanova, 2000; Clini, 2002; Clini, 1998), have not demonstrated reduced mortality in response to bilevel NIPPV therapy.

Comfort/Compliance Issues

Studies that reported intolerance due to high bilevel NIPPV pressure level settings included 2 shorter trials (Ambrosino, 1993; Nava, 1993) with brief acclimatization periods and 1 longer nocturnal study (Casanova, 2000), also with brief acclimatization periods, but lower bilevel pressure settings. Explanations for this may include patient/ventilator asynchrony resulting either from mask leak accompanying higher bilevel pressures, or increased inspiratory efforts/work due to breathing resulting from lower bilevel pressures. This may have also been the case in the 4 studies that reported sleep related difficulty (Garrod, 2000; Gay, 1996; Renston, 1994; Strumpf, 1991), which also used lower IPAP/EPAP bilevel pressure settings. Studies that reported mask/interface problems (Gay, 1996; Lin, 1996; Nava, 2001), or patient/ventilator asynchrony (Ambrosino, 1992; Lin, 1996; Vanpee, 2002b), were either shorter trials or had no acclimatization period.

The 3 month COPD study that had the lowest attrition rate due to comfort/compliance issues (1 out of 18 patients or 5.5%) in the bilevel NIPPV group had a 2 night bilevel NIPPV in-hospital acclimatization period, utilized daily diary cards regarding ventilator use and associated problems, and had outpatient clinic follow-up every 4 weeks (Meecham-Jones, 1995). Three longer COPD studies with trial periods of 6 months (Strumpf, 1991), one year (Casanova, 2000), 2 years (Clini, 2002), and 3 years

(Clini, 1998) reported greater comfort/compliance related attrition rates within the bilevel NIPPV groups. In the longest of these studies (Clini, 1998), 60% of the group had problems with NIPPV associated comfort issues such as nasal skin lesions, gastric distension, rhinorrhea, mucosal dryness, or skin inflammation. The length of time bilevel NIPPV was used (7.4±1.3 mean hours nightly for 3 years), and prior NIPPV use in 35 out of 39 of the subjects, likely contributed to the incidence of comfort related issues. This was the only COPD study in this systematic review that reported the actual incidence of each comfort related side effect in the study. It may be possible that the actual incidence of these complications may be greater in other studies. Despite the problems encountered, subjects in the Clini (1998) study had significantly improved exercise tolerance, reduced hospital stay and ICU admissions, all very desirable outcomes, which might seem to outweigh difficulty related to bilevel NIPPV use in subjects with CRF due to severe, advanced COPD.

Problems related to bilevel NIPPV compliance in the studies in this systematic review seem to be multifactoral. It is possible that a period of acclimatization, during which patients can be closely monitored and problems related to equipment and patient/mask interface issues can be managed, while titrating bilevel NIPPV pressure levels for both comfort and effectiveness, may be beneficial to improving compliance to bilevel NIPPV. Length of bilevel NIPPV trial also likely affects the accuracy of assessment of bilevel NIPPV effectiveness related to management of CRF in COPD.

Effectiveness of Bilevel NIPPV in the Restrictive Pulmonary Cohort

Respiratory Function

Bilevel NIPPV demonstrated consistent improvement in oxygenation (daytime $Pa0_2$ and nocturnal $Sa0_2$) in the restrictive pulmonary cohort. Although improvement in $PaC0_2$ was less consistent, there are indications that the use of bilevel NIPPV may slow the progression of worsening hypercapnia, and that this may occur to a greater extent in certain subsets of subjects with restrictive pulmonary disorders, i.e., those with a higher baseline $PaC0_2$ and/or those with kyphoscoliosis versus NMD. Subjects in the restrictive studies in this review that demonstrated substantial reductions in daytime PaC02 had higher baseline $PaC0_2$ values [Ergun (2002), 51.43mmHg; Nauffal (1996), 56.8 mmHg in kyphoscoliotic and 51.3 mmHg in neuromuscular disease groups; Strumpf (1990), 62.3 mmHg; Waldhorn (1992), 57.2 mmHg, respectively]. The study by Hill (1992), which showed little change in daytime $PaC0_2$ after a week of withdrawal, followed by resumption of bilevel NIPPV, showed significant worsening of nocturnal hypercapnia according to $PtC0_2$ monitoring, suggesting a preventative role for bilevel NIPPV related to the management of CRF in the restrictive pulmonary cohort. Nocturnal $PtC0_2$ monitoring, which is a more dynamic measure of gas exchange than daytime ABGs, may be a better measure of effectiveness of bilevel NIPPV for patients with restrictive lung disease with resulting alveolar hypoventilation as the underlying cause of their CRF.

Three studies (Fanfulla, 1997; Nauffal, 1996; Waldhorn, 1992), ranging from 3 months to 2 years, that assessed lung function in the restrictive pulmonary cohort , reported a slower than expected decline in FVC following a period of bilevel NIPPV, which may suggest a preventive role for bilevel NIPPV in slowing the rate of progressive decline of lung function in subjects with CRF due to restrictive pulmonary disorders. One possible explanation for this may be preservation of respiratory muscle function +/- reduced alveolar hypoventilation with bilevel NIPPV use.

Ergun (2002) showed reductions in EMGdi values, consistent with reduced WOB, which accompanied significant improvements in gas exchange, dyspnea, and exercise tolerance. Although the reduction in EMGdi did not reach statistical significance, NIPPV may have reset the respiratory center, thereby reducing central fatigue, as suggested by reduced hypercapnia and dyspnea, as well as improved exercise tolerance after 15 days (Meyer, 1994).

In the Nauffal (1996) study, significant improvements in hypercapnia (daytime and nocturnal) were associated with non-statistically significant increases in lung volumes and indices of respiratory muscle strength/endurance in the kyphoscoliosis group, whereas the neuromuscular disease/ALS group on the other hand, demonstrated very little improvement in hypercapnia, and reductions in lung volumes and indices of respiratory muscle strength/endurance. Both groups showed significant improvements in nocturnal SaO_2. Some relief of the mechanical disadvantage imposed by reduced chest wall and lung compliance with nocturnal bilevel NIPPV in the kyphoscoliosis group may be responsible for the improved lung volumes and indices of and respiratory muscle strength, and gas exchange. The nature of the problem underlying restrictive pulmonary disease and CRF in the ALS group, on the other hand, would be less likely to respond to bilevel NIPPV with sustained daytime improvement of gas exchange, indices of lung function and respiratory muscle strength, due to the functional disadvantage imposed by ongoing progression of intrinsic respiratory muscle weakness (Turkington, 2000).

Health-Related Outcomes

The restrictive studies in this systematic review that measured dyspnea and symptom relief consistently demonstrated relief of dyspnea and symptoms of chronic alveolar hypoventilation with bilevel NIPPV use. There were significant improvements in the 4 restrictive studies that assessed dyspnea, which were also accompanied by improvements in gas exchange. Significantly worsened daytime and nocturnal gas exchange, sleepiness score, and total sleep time, were accompanied by increasing daytime somnolence after withdrawal of nocturnal bilevel NIPPV for 1 week, in the study by Hill (1992). The results of these studies are consistently indicative of a supportive and preventative role for bilevel NIPPV in those individuals with restrictive pulmonary disorders who require management of sleep hypoventilation and central fatigue, dyspnea, and the distressing symptoms resulting from CRF.

No restrictive studies in this review formally assessed Functional Status/ADL. HRQOL was measured in only 1 restrictive pulmonary study, which showed more areas of improvement in the kyphoscoliosis versus the NMD group in response to bilevel NIPPV. The discrepancy between improvement in quality of life in the 2 groups may be due to the motor handicap in the NMD group, with a lack of improvement in hypercapnia and the associated distressing, ongoing symptoms related to chronic alveolar hypoventilation.

Very few of the studies assessed the impact of bilevel NIPPV on morbidity and/or mortality in restrictive lung disease. One study in this systematic review (Nauffal, 2002), which did show a significant reduction in hospital rate/year, also had significant improvement in HRQOL related outcomes, dyspnea, and gas exchange. The associated reduced morbidity, which accompanied improvement in clinical and functional outcomes in this study, may suggest a supportive role for subjects who respond well to bilevel NIPPV, related to management of the morbidity associated with CRF due to restrictive lung disease.

Effectiveness of Bilevel NIPPV in the Mixed Cohorts

The mixed study by Restrick (1993) was the only study in this systematic review that specifically compared bilevel NIPPV modes. Significant improvement in gas exchange (both $Pa0_2$ and $PaC0_2$) on the S mode, and some improvement in the ST mode, although not statistically significant, were found in the mixed COPD and restrictive groups, which might suggest that the spontaneous mode of bilevel NIPPV without a back-up rate was sufficient to improve alveolar hypoventilation in both these cohorts. However, there was no statistically significant difference for the reduction in mean nocturnal $PtC0_2$ between the 2 modes. In the restrictive group, who often have profound respiratory muscle weakness, the need for a back-up rate/timed mode requires assessment with a sleep study to determine how much REM desaturation is present and to what extent it is improved on a bilevel NIPPV S versus ST mode.

Bilevel NIPPV pressure levels used in the mixed study by Elliott (1995) were generally higher than in the study by Restrick (1992). The restrictive group in the Elliott (1995) mixed study, which used an ST bilevel mode and higher bilevel IPAP/EPAP pressures, showed significant improvement in both nocturnal $Sa0_2$ and $PtC0_2$ when EPAP of 5 cmH_20 was added, while the restrictive subjects in the Restrick (1993) study did not report significant improvement in gas exchange, likely due to the use of lower slightly lower bilevel NIPPV pressures, which may not have been sufficient to reduce alveolar hypoventilation. No other restrictive studies in this review specifically compared effectiveness of pressure levels for the restrictive group.

During REM sleep, nocturnal $PtC0_2$ reduction with the addition of EPAP in the COPD group in the mixed study by Elliott (1995) was greater in patients with a larger IPAP/EPAP pressure difference, which was consistent with the COPD cohort in the study by Vanpee (2002a), that showed a greater improvement in hypercapnia in COPD subjects with bilevel NIPPV pressure levels of 20/5 cmH_20 than with higher EPAP when using pressure levels of 20/10 cmH_20, suggesting maximal effectiveness when the amount of EPAP added is closest to, but not in excess of PEEPidyn (Vanpee, 2002a). Both of these mixed studies included very brief bilevel NIPPV trials [Elliott (1995), 2 nights; Restrick (1993), 3 nights], which may not be sufficient to determine long term outcomes.

Implications of Findings

Implications for Research

There were a number of factors contributing to heterogeneity of the studies included in this systematic review, which if addressed in future studies, may assist in allowing for more comprehensive meta-analyses related to bilevel NIPPV effectiveness in CRF due to COPD and restrictive pulmonary disease. More consistency with respect to inclusion and length of bilevel NIPPV acclimatization periods for future studies, may assist in reducing some of the factors that could potentially confound assessment of bilevel NIPPV effectiveness among the studies. Initiation of bilevel NIPPV was conducted in a variety of settings including tertiary, outpatient clinic, and home settings. Initiation of bilevel NIPPV should be done in hospital where possible, with comprehensive outpatient follow-up.

Consensus among researchers regarding use of consistent measurement tools and units of measure for the commonly studied outcomes related to bilevel NIPPV effectiveness in the management of CRF due to COPD or restrictive lung disease, would create the opportunity for a more comprehensive meta-analysis.

Inclusion of both static (ABGs) and dynamic (nocturnal $Sa0_2$ and $PtC0_2$) gas exchange outcome measures in the assessment of the effectiveness of bilevel NIPPV related to CRF resulting from nocturnal alveolar hypoventilation, would allow a more comprehensive assessment of gas exchange.

There was only one study in this systematic review (a mixed study) that formally compared modes of bilevel NIPPV. Future studies to assess the most effective mode of bilevel NIPPV in the COPD and restrictive pulmonary cohorts would be of benefit.

More long-term studies with larger sample sizes are needed to clarify whether there is a supportive/preventive role for bilevel NIPPV in management of symptoms and alteration/reduction of morbidity and mortality related to disease progression and resulting CRF in both COPD and restrictive pulmonary cohorts.

Larger randomized controlled studies focusing on improvement of outcomes related to bilevel NIPPV use in CRF due to severe stable COPD are also needed. If it is possible to consider disease severity in analysis related to assessment of the effectiveness of bilevel NIPPV in future studies, this may assist in clarifying whether there is a subset/subgroup of responders within the COPD cohort.

Studies comparing non-bilevel NIPPV to bilevel NIPPV are needed to assist in clarifying which type of NIPPV would be the most efficacious with respect to management of CRF for patients with restrictive pulmonary disease. It would be preferable that future studies be randomized controlled trials; however, it is recognized that ethical issues related to such studies in the restrictive cohort may preclude use of a randomized design. More studies are also needed related to the extent of bilevel NIPPV effectiveness in managing CRF according to type and progression (rapid, progressive, or slow/non-progressive) of the NMD underlying the restrictive pulmonary disorder. Outcomes that were absent or least studied in the restrictive studies in this review, that would merit assessment in future studies, include morbidity and mortality.

Implications for Practice

The results of this systematic review are indicative that there is a supportive and preventive role for bilevel NIPPV in the adjunctive management of CRF in a subset of responders with severe stable COPD associated with comorbid changes in gas exchange, exercise tolerance and functional status/ADL, imposed on them by nocturnal alveolar hypoventilation (despite the absence of OSA and/or OHS), chronic dyspnea and increased work of breathing due to lung hyperinflation/PEEPidyn, and increased inspiratory mechanical load.

The effectiveness of nocturnal bilevel NIPPV support in severe stable COPD is proportionate to IPAP/EPAP pressure levels, which should be titrated for a pressure difference sufficient to increase ventilation/VT and reduce hyperinflation/PEEPidyn, with Fi02 entrained as necessary to maintain adequate oxygenation. Ideally, individual titration of bilevel NIPPV should be initiated in hospital where possible, to ensure an observation period to monitor response during acclimatization, at which time problems with mask interface and/or asynchronous breathing can be managed. Bilevel NIPPV can be used preventatively in some, but not all patients with severe, stable, chronically decompensated COPD, to reduce frequency of hospital admissions, contributing to subsequent reductions in utilization of health care resources and expenditures.

Improvement and/or delay of progressive decline in FEV1 and FEV1/FVC related to bilevel NIPPV use is not a realistic goal in severe stable COPD, as bilevel NIPPV can temporize and relieve airflow obstruction nocturnally during use; however bilevel NIPPV use cannot reverse the lung parenchymal changes of the disease. Bilevel NIPPV has not been shown to reduce mortality.

The observational restrictive pulmonary studies in this systematic review suggest that there is a supportive role for bilevel NIPPV in management of impaired gas exchange, sleep disruption, symptoms of daytime sleepiness, and dyspnea related to reduced chest wall and lung compliance, that places patients with restrictive pulmonary disorders at a mechanical disadvantage. Bilevel NIPPV in this setting has not consistently shown improvement in lung volumes in response to bilevel NIPPV, but may slow progression of decline in lung function in some restrictive pulmonary patients with NMD. Reduction in frequency of hospital admissions for patients with restrictive lung disease supports a preventative role for bilevel NIPPV in the management of CRF. Within the restrictive pulmonary cohort, there are some patients who benefit less than others from the use of bilevel NIPPV for management of CRF, including NMD and ALS patients with bulbar weakness and upper airway resistance.

Conclusion

Patients with severe stable COPD and restrictive pulmonary disorders who lack the necessary respiratory reserve to respond to minimal increases in ventilatory demand due to their altered lung dynamics are constantly on the verge of respiratory decompensation. Based on the results of this systematic review, bilevel NIPPV use in severe stable COPD can significantly improve gas exchange, exercise tolerance, dyspnea and increased work of breathing due to lung hyperinflation/PEEPidyn, frequency of hospitalization, HRQOL, and functional status/ADL, in some, but not all patients. This suggests a supportive and preventive role for the use of bilevel NIPPV in the management of CRF. The effectiveness of bilevel NIPPV used nocturnally and/or as necessary during the daytime in some individuals with severe advanced COPD, however, is of benefit for intermittent reduction in work of breathing and respiratory muscle rest, which in turn contributes to improved exercise tolerance on a short term day to day basis.

Inconsistency related to effectiveness in all outcomes assessed with bilevel NIPPV use in severe stable COPD, may be due to variability in the bilevel NIPPV pressure levels used, hours of use, and degree of hyperinflation/PEEPidyn. Sleep and pulmonary function are not improved with bilevel NIPPV due to comfort/equipment issues and nature of the disease. Lung volumes, alveolar ventilation and work of breathing are improved during bilevel NIPPV use, however the improvement is not consistently sustained following use. Bilevel NIPPV was not shown to reduce mortality in the COPD cohort.

With bilevel NIPPV use, patients with restrictive pulmonary disease demonstrated improvement in gas exchange, sleep, symptoms of daytime sleepiness, and dyspnea related to reduced chest wall and lung compliance, based on observational data. There may be a preventive role related to slowing the progression of decline in lung function and improvement in exercise tolerance in the restrictive pulmonary disease cohort, however there is insufficient data to conclude this at present. There were no RCTs examining the effectiveness of bilevel NIPPV in the restrictive pulmonary cohort.

When outcomes included in the assessment of the effectiveness of bilevel NIPPV address the mechanical disadvantage (inspiratory mechanical load), alveolar hypoventilation, lung hyperinflation, as well as parenchymal changes (alveolar destruction and loss of functioning lung units/airway obstruction) that preceeds the mechanical disadvantage, bilevel NIPPV has a supportive and preventative role in the management of CRF in some individuals with COPD and restrictive pulmonary disorders. Just as the effectiveness of bilevel NIPPV in restrictive pulmonary disease was found to be inconsistent with respect to NMD conditions within the restrictive pulmonary disease cohort, so also is the effectiveness in severe stable COPD likely limited to a certain subset within this cohort (patients with chronic hypercapnic respiratory failure and increased PEEPidyn). Use of bilevel NIPPV in the COPD and restrictive pulmonary cohorts should be offered to those individuals who demonstrate benefit according to improvement in outcomes related to the distressing and debilitating effects of CRF due to disease progression.

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Appendix A

Randomized Controlled Trial Validity - Tool Part 1

Estabrooks, et al. (1999) A systematic Review of Structured Consumer Decision Aids, Technical Report: Institute for Clinical Evaluative Studies, Toronto.

Reviewer: ______________________ **Date:** ______________________

Systematic Review [illegible]
RCT Validity

Study: ______________________
Publication Date: ______________

First Author: ______________________
Journal: ______________________

DESIGN AND ALLOCATION:

Description of randomizaton was:

adequate	2
partial	1
inadequate	0

Do you believe there could have been bias in the intervention assignment?

yes	0
not likely	1
no	2

Was group equivalence assessed post hoc?

yes	1
no	0

Design and Allocation Sub-Total ______/5

RECRUITMENT:

Is sampling process adequately described?

yes	1
no	0

Was the participation rate clearly described?

yes	1
no	0

What was the attrition rate?

<20%	2
21-50%	1
>50%	0

Was there an appropriate sample size justification?

yes	2
no	0

Recruitment Sub-Total ______/6

INCLUSION AND EXCLUSION:

Were the inclusion/exclusion criteria clearly defined?

yes	2
partial	1
no	0

Do we know how many eligible patients were excluded from the trial?(Not enrolled for logistical reasons, refused consent, etc.)

yes	2
partial	1
no	0

Inclusion and Exclusion Sub-Total ______/4

DESCRIPTION OF INTERVENTION:

Was the intervention fully described for the treatment group?

yes	2
partial	1
no	0

Was the intervention fully described for the control group?

yes	2
partial	1
no	0

Description of Intervention Sub-Total ______/4

STATISTICAL ANALYSIS:

Test Stated?	yes	1
	no	0
P-value and/or C.I.	yes	1
	no	0

Is the statistical analysis appropriate?

yes	1
no	0

Was there an atttempt to control statistically for confounders?

yes/NA	1
no	0

Are the conclusions drawn reasonable and supported by the data?

yes	2
somewhat	1
no	0

Statistical Analysis Sub-Total ______/6

Appendix B

Randomized Controlled Trial Validity - Tool Part 2

Estabrooks, et al. (1999) A systematic Review of Structured Consumer Decision Aids, Technical Report: Institute for Clinical Evaluative Studies, Toronto.

OUTCOME MEASUREMENT:

Are outcome measures (dependent variables) clearly defined?

yes	2
somewhat	1
no	0

Is data collection protocol clearly described?

yes	2
somewhat	1
no	0

Is past reliability and validity of measurement tools reported?

yes	2
somewhat	1
no	0

Is current reliablity and validity of tools reported?

yes	2
somewhat	1
no	0

Is the timing outcome assessments appropriate?

>2 post measures	2
2 post measures	1
only 1 post	0

Code "0" if post measures inappropriately timed
Code "1" if only 1 post measure but sound rationale

Outcome Measurement Sub-Total ______/10

CALCULATION OF VALIDITY SCORE:

Categories	Sub-Total	Rating
Design and Allocation (5)	______	______
Recruitment (6)	______	______
Inclusion and Exclusion (4)	______	______
Description of Intervention (4)	______	______
Statistical Analysis (6)	______	______
Outcome Measurement (10)	______	______
Total	______	______

SUBSCALE AND VALIDITY RATING

Design and Allocation

0-1	LO
2-3	MED
4-5	HI

Recruitment

0-2	LO
3-4	MED
5-6	HI

Inclusion and Exclusion

0-1	LO
2-3	MED
4	HI

Description of Intervention

0	LO
1-2	MED
3-4	HI

Statistical Analysis and Conclusions

0-2	LO
3-4	MED
5-6	HI

Outcome Measurement

0-4	LO
5-7	MED
8-10	HI

OVERALL VALIDITY RATING

≥LO	LO
<2LO, <3HI	MED
≥3HI, 0 LO	HI

Appendix C

Observational Validity Tool Part 1

Estabrooks, et al. (1999) A systematic Review of Structured Consumer Decision Aids, Technical Report: Institute for Clinical Evaluative Studies, Toronto.

Reviewer: ______________________ **Date:** __________

[illegible]

Study: ______________ **First Author:** ______________

Publication Information Date: ________ **Journal:** ______________

Study Design:	**No/unsure**	**Yes**
Was sample size justified?	0	2
One of a, b, or c:		
a) One pre-test and several post-test measures	0	2
b) Simple before-and-after study	0	1
c) Post only (or no comparison pre to post)	0	0
Does the study employ an a priori comparison strategy?		
i) Subjects are assigned to non-equivalent groups	0	1
ii) Attempt to create equivalence by matching	0	1
Sub-total	______	(6)

Inclusion and Follow-up	**No/unsure**	**Yes**
Is sample clearly described?	0	1
Are participants likely to be representative of relevant population	0	1
Is attrition rate described (if no attrition code 1)	0	1
Is there rationale given for length of time between pre and lost post intervention measure	0	1
Sub-total	______	(4)

Control of Confounders?	**No/unsure**	**Yes**
Are preexisting differences between study participants assessed	0	1
Do all subjects in treatment group receive same treatment	0	1
Do all subjects in other group(s) receive same intervention (if n/a code 1)	0	1
Does study employ self report in addition to standardized tests to measure treatment effectiveness	0	1
Sub-total	______	(4)

Appendix D

Observational Validity Tool Part 2

Estabrooks, et al. (1999) A systematic Review of Structured Consumer Decision Aids, Technical Report: Institute for Clinical Evaluative Studies, Toronto.

Data Collection and Outcome Measurement	**No/unsure**	**Yes**
Is the intervention (decision aid) well described	0	1
Are outcome measures well described	0	1
Is data collection protocol described well	0	1
Is past reliability and/or validity of measurement tools reported	0	1
Is reliability and/or validity of current investigator designed measurement tools reported	0	2
Sub-total	______	(6)

Statistical Analysis and Conclusions	**No/unsure**	**Yes**
Tests stated	0	1
P value and/or C.I.	0	1
Are correct statistical analysis used	0	1
Are study conclusions reasonable and supported by the data	0	1
Does the analysis attempt to assess for equivalence of subjects/groups	0	1
Is there an analysis that attempts to control for confounders statistically	0	1
Sub-total	______	(6)

Discussion	**No/unsure**	**Yes**
Design limitations are discussed	0	1
Design rationale is discussed	0	1
Sub-total	______	(2)

Categories	**Subtotal**
Study Design	______/6
Inclusion and Follow-up	______/4
Control of Confounders	______/4
Data Collection and Outcome Measurement	______/6
Statistical Analysis and Conclusions	______/6
Discussion	______/2
Total:	______/28

Validity Ratings	**LO**	**MED**	**HI**
Study Design	0-1	2 - 4	5 - 6
Inclusion and Follow-up	0	1 - 2	3 - 4
Control of Confounders	0	1 - 2	3 - 4
Data Collection and Outcome Measurement	0 - 2	3 - 4	5 - 6
Statistical Analysis and Conclusions	0 - 2	3 - 4	5 - 6
Discussion	0	1	2

Overall Validity Rating		**Equals**
	≥2 LO	LO
	<2 LO, <3 HI	MED
	≥3 HI, 0 LO	HI

RATING: ______

Appendix E

Data Extraction Tool Part 1

Estabrooks, et al. (1999) A systematic Review of Structured Consumer Decision Aids, Technical Report: Institute for Clinical Evaluative Studies, Toronto.

Reviewer: ____________________ **Date:** ______________

[redacted] **DATA EXTRACTION TOOL** [redacted]

Study #: ________________ **First Author:** ______________

Publication Information: **Date:** _____

Journal: ____

Data Collected From . . . ________ to ______ **Not described:** ☐

Country of Study?

1. Canada
2. United States
3. Other ______________

Prospective?

1. Prospective
2. Not prospective

Study Design?

1. Experimental (ie, randomized to groups)
2. Quasi-experimental (ie, non-equivalent groups, no randomization)
3. Before/After (same individuals, one group only)
4. Before/After (different individuals)
5. Cross-sectional (eg, survey)
6. Other: ______________________________
7. Cannot determine

Authors description of study design: ___________________________

Sampling:

1. Convenience (eg: not purposive)
2. Purposive, describe: ______________________________ (eg: sequential)
3. Other: ______________
4. Cannot determine

Sample size at baseline?

Total sample size:	_____	0 (unknown)
Number of groups:	_____	0 (unknown)
Control Group:	_____	0 (unknown)
Experimental Goups:	_____	0 (unknown)
	_____	0 (unknown)
	_____	0 (unknown)

Sample size at last post-intervention measurement?

Total sample size:	_____	0 (unknown)
Number of groups:	_____	0 (unknown)
Control Group:	_____	0 (unknown)
Experimental Goups:	_____	0 (unknown)
	_____	0 (unknown)
	_____	0 (unknown)

Appendix F

Data Extraction Tool Part 2

Estabrooks, et al. (1999) A systematic Review of Structured Consumer Decision Aids, Technical Report: Institute for Clinical Evaluative Studies, Toronto.

If survey, response rate: ________

Sample size rationale present? yes ☐ no ☐

TYPES OF ANALYSIS:

1. Chi Square
2. T-test
3. ANOVA, ANCOVA
4. MANOVA, MANCOVA
5. Regression/multiple regression
6. Descriptive
7. Other ________________

Sample characteristics	Group 1 (experimental)	Group 2 (control)	Group 3 or Total
(1) Sex			
(2) Age			
(3) Education ______			
(4) Ethnicity			
(5) Disease condition, characteristic, co-morbidity, etc.			
Other:			

DESCRIBE THE STUDY DESIGN

Appendix G

Data Extraction Tool Part 3

Estabrooks, et al. (1999) A systematic Review of Structured Consumer Decision Aids, Technical Report: Institute for Clinical Evaluative Studies, Toronto.

Describe the intervention in detail:

Control group "intervention" (brief description)

Describe the Outcome measure or evaluation process

Table 1

Detailed Search Summary - Part 1

Database Search Terms	Limits	Date	Database	Hits	Abstracts Reviewed	Abstracts Excluded	Abstracts Retained
bilevel OR bi-level airway pressure OR bi-level CPAP OR biphasic positive airway pressure OR nasal ventilation OR positive pressure ventilation OR NIPPV	Multiple database search including MEDLINE, PreMEDLINE, all EBM Reviews(CDSR, ACP Journal Club, DARE, CRCT), CINAHL, EMBASE;Deduped to remove duplicates.	22-Feb-03				Duplicate, invasive, not bi-level ventilation, non-english, reviews.	
	Years 1980 to 2003		**Medline**	2304	181	88	93
			Premedline	20			
			EBM Reviews				
			CDSR	51	2	2	0
			ACP Journal Club	11	0	0	0
			DARE	6	0	0	0
			CRCT	294	47	21	26
			CINAHL	604	17	13	4
			EMBASE	613	85	56	29
			OCLC PAPERS FIRST	181	26	15	11
			Biological Abstracts	0	0	0	0
		Total		**4084**	**358**	**195**	**163**
Manual Search							
Journals	Years 2001 - 2003						5
Reviews	Years 1980 - 2003						7
		Total					**175**

Table 2
Detailed Search Summary - Part 2

Database Search Terms	Limits	Date	Database	Hits	Abstracts Reviewed	Abstracts Excluded	Abstracts Retained
bilevel OR bi-level airway pressure OR bi-level CPAP OR biphasic positive airway pressure OR nasal ventilation OR positive pressure ventilation OR NIPPV	Multiple database search including MEDLINE, PreMEDLINE, all EBM Reviews(CDSR, ACP Journal Club, DARE, CRCT), CINAHL, EMBASE;Deduped to remove duplicates.	6-Dec-03				Duplicate, invasive, not bi-level ventilation, non-english, reviews.	
	Years 1980 to 2003		**Medline & Premedline**	87	4	3	1
			EBM Reviews				
			CDSR	6	0	0	0
			ACP Journal Club	0	0	0	0
			DARE	7	0	0	0
			CRCT	0	0	0	0
			CINAHL	36	1	1	0
			EMBASE	69	5	4	1
			OCLC PAPERS FIRST	0	0	0	0
			Biological Abstracts	0	0	0	0
		Total		**205**	**10**	**8**	**2**
Manual Search							
Journals	Feb 2003 to Dec 2003						0
Reviews	Feb 2003 to Dec 2003						0
		Total					**2**

Table 3
Search Summary

Date	Abstracts Retained		Number of Papers Screened for Inclusion	Number of Papers Excluded	Number of Papers Included
	Database Search	Manual Search			
22-Feb-03	163	12	175	144	31
6-Dec-03	2	0	2	1	1
Totals	165	12	177	145	32

Table 4
COPD Study Design and Conditions

Pub Date	First Author	NIPPV Trial	Study Type	Run-In or Acclimatization	Previous NIPPV or Vent	Hours of NIPPV Noct(N)/Day(D)	Gas Exchange	
							PaO2	PaCO2
				COPD RCTs				
2000	Casanova,C	1 year	BS RM	2 nights	NR	5.9-6.2hrs/N	56.6	51.9
2002	Clini,E	2 years	BS RM	1mo/OP;10dysIP	NR	>5 hrs-9(2)hrs/N,D	<60	>50
2002	Diaz, O	3 weeks	BS BA	2 weeks	No	3hrs/dayx5D/wk	<60	>50
2000	Garrod,R	8 weeks	BS RM	4 weeks	No	8 hrs or > /N	65.4(9.07)	45.6(7.79)
1996	Gay,PC	3 mos	BS BA	1.5 days	No	5.1(3.8) hrs/N	66.4	54.7
1994	Renston,JP	5 days	BS BA	None	No	2 hrs/D x 5 D	75	48
				COPD OBSERVATIONAL STUDIES - NIPPV TRIAL OF 1 WEEK OR LESS				
1992	Ambrosino,N	2 days	CSVR RM	None	No	2 hrs/D x 2 D	50	61
1993	Ambrosino,N	3 days	NCSVR BA	2 weeks Acclim	No	10min/mode x 4	49	56
1998	Bianchi,K	2 days	NCSVR RM	1 week Acclim	No	4 endur tests/2 D	51.75	51.75
1997	Krachman,SL	3 nights	CSVR BA	1 night Acclim	No	3.5 hrs or >/N	92	58
1993	Lien,TC	40 min	CSVR BA	None	No	40 min ea vent	66	45
1997	Marangoni,S	1 day	CSVR RM	1 week Acclim	NR	45 min ea vent	48.9	52.5
1993	Nava,S	1 day	CSVR RM	4wkRI;1wkAccli	No	5 x 15 min trials	48.3	57.3
2002a	Vanpee,D	1 day	NEG BS RM	None	NR	3 x 5 min trials	50	57
2002b	Vanpee,D	<1 week	NCSVR RM	None	No	Time not spec.	68.1	42.2
2000	Vitacca	1 day	NCSVR RM	2 weeks	31(20) months	5 hrs/N minimum	51.7	56.2
2003	Highcock,MP	3 days	CSVR RM	1st day	6/8 pts	2walks x 2days	69	52.5

Study Type

BA: Before/After

BS: Between Subjects

CSVR: Crossover

NCSVR: Noncrossover

NEG: Nonequivalent Groups

WS: Within Subjects

RM: Repeated Measures

Table 5
COPD and Restrictive Study Design and Conditions

Pub Date	First Author	NIPPV Trial	Study Type	Run-In or Acclimatization	Previous NIPPV or Vent	Hours of NIPPV Noct(N)/Day(D)	Gas Exchange	
							PaO2	PaCO2
COPD OBSERVATIONAL STUDIES - NIPPV TRIAL OF 1 TO 6 WEEKS								
1996	Lin,CC	6 weeks	CSVR RM	None	No	NOCT(Hrs NR)	51.7	50.5
2001	Nava,S	4 weeks	NEG BS BA	2 x 1 hr trials	No	6 hrs/N	53.26	56.73
COPD OBSERVATIONAL STUDIES - NIPPV TRIAL OF LONGER THAN 6 WEEKS								
1998	Clini,E	3 years	NEG BS RM	2 nights(5hrs/ea)	35/49	7.4(1.3) hrs/N	48.75	52.5
1995	Meecham Jones	3 months	CSVR BA	4 wkRI;2niteNIPV	No	6.9 hrs/N	45.3	55.8
1991	Strumpf,DA	6 months	CSVR RM	2-3 hrs	No	6.7hrs/N	64	46
RESTRICTIVE STUDIES - 1 WEEK OR LESS								
2002	Highcock,MP	3 days	WS BA	None	11-120 months	At least 5 hrs/N	78	45
2002	Highcock,MP	3 days	WS RM	None	6 - 83 months	Trdml walks /2 D	68.4	47.9
RESTRICTIVE STUDIES - 1 TO 6 WEEKS								
2002	Ergun,P	15 days	WS BA	None	NR	2 hrs/D x 15 D	64.1	51.43
1992	Hill,N	3 weeks	WS RM	1 month of BiPAP	2 months	BiPAP heldx8(2) D	65	70
RESTRICTIVE STUDIES - 1 TO 6 WEEKS								
1997	Fanfulla,F	2 years	WS RM	3 day Run-in	No	NOCT (Hrs NR)	78	44.3
1996	Nauffal,D	18 months	WS RM	In-hosp titration	No	7 hrs/N	Kyph/ NMD 57.5 / 70.6	Kyph/ NMD 56.8 / 51.3
1990	Strumpf,DA	2wk-5mos	WS BA	None	All (5 to 14mos)	NR	69.3	62.3
1992	Waldhorn,RE	3 months	WS RM	2 nites in-hosp	2 pts	NR	74	57.2

Study Type

BA: Before/After
BS: Between Subjects
CSVR: Crossover

NCSVR: Noncrossover
NEG: Nonequivalent Groups
WS: Within Subjects
RM: Repeated Measures

Kyph: Kyphoscoliosis
NMD: Neuromuscular disease
Noct: Nocturnal

Table 6
Mixed Study Design and Conditions

Pub Date	First Author	NIPPV Trial	Study Type	Run-In or Acclimatization	Previous NIPPV or Vent Use	Hours of NIPPV Noct(N)/Day(D)	Gas Exchange	
							PaO2	PaCO2
MIXED STUDIES								
1995.	Elliott,MW	2 nights	CSVR RM	3 hrs	Yes - All	COPD; 4.2 - 9.9 REST; 4.1 - 8.4	COPD/REST 46.3 / 68.8	COPD/REST 63.2 / 51.1
1993	Restrick,LJ	3 nights	NCSVR BA	3 nights	Yes - All	6 hrs/N	COPD/RST 52.5 / 61.5	COPD/RST 59.2 / 51.7

Study Type

BA: Before/After
RM: Repeated Measures

CSVR: Crossover
NCSVR: Noncrossover

REST: Restrictive
N: Nocturnal

Table 7
COPD Interventions

Pub Date	First Author	Lung Function			Ventilator Type(s)	Pressures (cmH20) Mean(SD)		O2 Use During
		FEV1	FVC	FEV1/FVC		IPAP	EPAP	Yes/No
COPD RCTs								
2000	Casanova,C	0.84L	2.1L	40%	DP-P	12(2)	4	49/52 pts
2002	Clini,E	27(8)%	55(17)%	49%	BP-P Respironics S	14(3)	2(1)	All
2002	Diaz, O	0.77L	2.17L	35%	BP-P Respironics ST	18(2)	min of 2	All
2000	Garrod,R	0.96L	2.24L	43%	BP-P Respironics ST	13-24	4 to 6	2/37 pts
1996	Gay,PC	0.62L	NR	34.60%	BP-P Respironics ST	10	2	6/7 pts
1994	Renston,JP	0.76L	NR	33%	BP-P Respironics ST	15-20	2	NR
COPD OBSERVATIONAL STUDIES - NIPPV TRIAL OF 1 WEEK OR LESS								
1992	Ambrosino,N	0.58L	NR	46%	BP-P Respironics S	22	0	No
1993	Ambrosino,N	NR	NR	39%	BP-P Respironics S	10 & 20	0 & 5	7/9 pts
1998	Bianchi,K	32%	50%	NR	BP-P Respironics S	12 to 16	1	All
1997	Krachman,SL	0.58	2.05	28%	BP-P Respironics ST	22(.3)	3(1)	All
1993	Lien,TC	0.71	2.01	35%	BP-P Respironics S	10	2	NR
1997	Marangoni,S	38.60%	NR	53.20%	BP-P Respironics S	19.4(2.2)	1 to 2	No
1993	Nava,S	20%	41.80%	35%	BIRD PSV	10 & 20	0 & 5	No
2002a	Vanpee,D	32%	60%	NR	BP-P Respironics ST	10 & 20	5 & 10	NR
2002b	Vanpee,D	32%	76%	NR	BP-P Respironics ST	15	5	No
2000	Vitacca	23%	40%	NR	BP-P Respironics	16(3)	3.1(1.6)	All
2003	Highcock,MP	1.0L	85%	34%	BP-P;N-P;SVP-P	9 to 16	min EPAP	NR

Ventilator Types
BIRD PSV: Bird
BP-P: BiPAP
DP-P: DP90 Taema, France
N-P: Nippy
SVP-P: Sullivan VPAP

Ventilator Modes
S: Spontaneous Bilevel
ST: Spontaneous/Timed Bilevel
T: Timed Bilevel
PSV: Pressure Support Ventilation

L: Liters
NR: Not reported

Table 8
COPD and Restrictive Interventions

Pub Date	First Author	Lung Function			Ventilator Type(s)	Pressures (cmH20) Meaan(SD)		O2 Use During
		FEV1	FVC	FEV1/FVC		IPAP	EPAP	Yes/No
COPD OBSERVATIONAL STUDIES - NIPPV TRIAL OF 1 TO 6 WEEKS								
1996	Lin,CC	35%	45%	55%	BP-P Respironics S	8 to 15	<2	All
2001	Nava,S	0.69L	NR	36.30%	BP-P Respironics S	max tol	no > 4	All
COPD OBSERVATIONAL STUDIES - NIPPV TRIAL OF LONGER THAN 6 WEEKS								
1998	Clini,E	31%	57%	46%	BP-P Respironics ST	10 to 16	2 to 4	All
1995	Meecham Jones	0.86L	2.03L	42%	BP-P Respironics S	16 to 22	2 to 4	All
1991	Strumpf,DA	0.54	1.71	32%	BP-P Respironics ST	15(1)	2	6/7 pts
RESTRICTIVE STUDIES - 1 WEEK OR LESS								
2002	Highcock,MP	0.7(24%)	1.1(27%)	NR	QP-P, SVP-P (ST)	21(3.5)	min EPAP	No
2002	Highcock,MP	0.7L	1.0L	NR	BP-P;N-P;SVP-P;ST	13.7(4.8)	min EPAP	NR
RESTRICTIVE STUDIES - 1 TO 6 WEEKS								
2002	Ergun,P	NR	36.70%	94%	Moritz II Bilevel,MAP	10 to 15	4	5/7 pts
1992	Hill,N	0.87L	0.97L	NR	BP-P Respironics ST	12 to 16	0 to 6	2/6 pts
RESTRICTIVE STUDIES - 1 TO 6 WEEKS								
1997	Fanfulla,F	NR	VC 752.5	NR	BP-P Respironics S	12 to 16	0 to 6	All
1996	Nauffal,D	Kyph; NMD 37.5%/38%	Kyph; NMD 42%/37.5%	TLC 63 / 53	DP-90, Taema	min of 10	min of 4	19/35 Kyph
1990	Strumpf,DA	NR	VC 1.28	NR	BP-P Respironics T	%IPAP;40	2 to 8	NR
1992	Waldhorn,RE	0.62	0.73	NR	BP-P Respironics S	12 to 18	2 to 4	1/8 pts

Ventilator Types
BIRD PSV: Bird
BP-P: BiPAP
DP-P: DP90 Taema, France
N-P: Nippy
SVP-P: Sullivan VPAP

Ventilator Modes
S: Spontaneous Bilevel
ST: Spontaneous/Timed Bilevel
T: Timed Bilevel
PSV: Pressure Support Ventilation

Kyph: Kyphoscoliosis
L: Liters
NMD: Neuromuscular Disease
NR: Not reported

Table 9
Mixed Study Interventions

Pub Date	First Author	Lung Function			Ventilator Type(s)	Pressures (cmH20)		O2 Use During
		FEV1 L	FVC L	FEV1/FVC		IPAP	EPAP	Yes/No
MIXED STUDIES - SIX WEEKS AND LONGER								
1995	Elliott,MW	COPD/RST	COPD/RST	COPD/RST	BP-P Respironics	20 COPD	7.3 COPD	No
		0.46 / 0.78	1.89 / 1.06	NR		18.9 KYPH	5 KYPH	
1993	Restrick,LJ	COPD/RST	COPD/RST	COPD/RST	BP-P Respironics ST	15 COPD	2 COPD	Yes
		0.6 / 0.7	1.8 / 1.3	NR		16 KYP	2 KYP	

Ventilator Types

BP-P: BiPAP

Ventilator Modes

ST: Spontaneous/Timed Bilevel

Disease Type

COPD: Chronic obstructive lung disease
Kyph: Kyphoscoliosis
RST: Restrictive

Table 10
Data Extraction - COPD Studies

COPD RANDOMIZED CONTROLLED TRIALS										
BETWEEN SUBJECTS - BEFORE/AFTER DESIGN										
Pub Date	First Author	Data Coll	Pro/ Retro	Study Design	Sample Type	Sample Characteristics		Enrolled	Randomized	Completed
						Sex (M/F)	Age			
2002	Diaz,O	ND	P	BS,BA	C	13/5;15/3	67(8);67(7)	56	36	36
1996	Gay,PC	1996	P	BS,BA	C	5/2;5/1	71.0;66.5	35	13	10
1994	Renston,JP	ND	P	BS,BA	C	3/6;3/5	62;68	17	17	17
BETWEEN SUBJECTS - REPEATED MEASURES DESIGN										
2000	Casanova,C	1995-1997	P	BS,RM	C	20/0;23/1	64(5);68(4)	80	52	44
2002	Clini,E	1996-2000	P	BS,RM	C	32/7;37/10	64(7);66(14)	122	86	47
2000	Garrod,R	ND	P	BS,RM	C	17;20	63;67	45	45	37
OBSERVATIONAL STUDIES										
CROSSOVER STUDIES - BEFORE/AFTER										
1997	Krachman,SL	ND	P	CSVR,WS,BA	C	5M/1F	63(6)	6	6	6
1995	Meecham Jones	ND	P	CSVR,WS,BA	C	15M/3F	69(43-74)	18	18	14
CROSSOVER STUDIES - REPEATED MEASURES										
1992	Ambrosino,N	ND	P	CSVR,WS,RM	C	7M	64.6(11.6)	7	7	7
1993	Lien,TC	ND	P	CSVR,WS,RM	C	11M	69(5)	11	11	11
1996	Lin,CC	1990-1994	P	CSVR,WS,RM	C	7M/5F	65(8)	17	12	10
1997	Marangoni,S	ND	P	CSVR,WS,RM	C	11M/3F	62.9(9.8)	14	14	14
1993	Nava,S	ND	P	CSVR,WS,RM	C	5M/2F	59.5(8.1)	7	7	6
1991	Strumpf,DA	ND	P	CSVR,WS,RM	C	19M/4F	66(1)	23	19	7
2003	Highcock,MP	ND	P	CSVR,WS,RM	C	6M/2F	66(8)	8	8	8

Age: Reported as mean(SD)

BA: Before/After
BS: Between Subjects
CSVR: Crossover

NEG: Nonequivalent Groups
RM: Repeated Measures
WS: Withtin Subjects

Data Collection: ND - Not described
Prospective/Retrospective: P - Prospective
Sample Type: C - Convenience

M: Male
F: Female

Table 11
Data Extraction - COPD Studies

Pub Date	First Author	Data Coll	Pro/ Retro	Study Design	Sample Type	Sample Characteristics		Enrolled	Included	Completed
						Sex (M/F)	Age			
COPD OBSERVATIONAL STUDIES										
NONCROSSOVER - WITHIN SUBJECTS - BEFORE/AFTER DESIGN										
1993	Ambrosino, N	1 DA	P	WS,BA	C	8M/1F	47 - 67	9	7	7
NONCROSSOVER - WITHIN SUBJECTS - REPEATED MEASURES DESIGN										
1998	Bianchi, K	ND	P	WS,RM	C	14/1	64(8)	15	15	15
2002b	Vanpee, D	ND	P	WS,RM	C	9M/1F	63(10)	10	10	10
2000	Vitacca, M	1998-1999	P	WS,RM	C	21M/2F	68(5)	23	23	23
NONEQUIVALENT GROUP TRIALS										
BETWEEN SUBJECTS - BEFORE/AFTER DESIGN										
2001	Nava,S	ND	P	NEG,BS,BA	C	ND	67.7(6.5)	23	22	22
BETWEEN SUBJECTS - REPEATED MEASURES DESIGN										
1998	Clini,E	3 yrs	P	NEG,BS,RM	C	22/6;14/7	66(6); 66(8)	49	49	UC
2002a	Vanpee, D	ND	P	NEG,BS,RM	C	ND	60(12.5)	20	20	20

Age; Reported as mean(SD)

BA: Before/After
BS: Between Subjects
CSVR: Crossover

NEG: Nonequivalent Groups
RM: repeated Measures
WS: Withti Subjects

Data Collection: ND - Not described
Prospective/Retrospective: P - Prospective
Sample Type: C - Convenience

M: Male
F: Female
ND: Not described
UC: Unclear

Table 12

Data Extraction Restrictive and Mixed Studies

Pub Date	First Author	Country	Data Coll	Pro/ Retro	Study Design	Sample Type	Sample Characteristics		Enrolled	Completed
							Sex (M/F)	Age		
RESTRICTIVE OBSERVATIONAL STUDIES										
NONCROSSOVER - WITHIN SUBJECTS - BEFORE/AFTER DESIGN										
2002	Ergun,P	Turkey	ND	P	WS,BA	C	10M/2F	66.2(11.5)	12	12
2002	Highcock,MP	Camb,UK	ND	P	WS,BA	C	7M/3F	NS	10	10
1990	Strumpf,DA	US	ND	P	WS,BA	C	2M/2F	31,41,50,57	4	4
NONCROSSOVER - WITHIN SUBJECTS - REPEATED MEASURES DESIGN										
1997	Fanfulla,F	Italy	ND	P	WS,RM	C	NS	18.3(15-22)	10	7
2002	Highcock,MP	UK	ND	P	WS,RM	C	5M/3F	64(3.6)	8	8
1992	Hill,N	US	ND	P	WS,RM	C	1M/5F	51(6)	6	6
1996	Nauffal,D	Spain	1997-2000	P	WS,RM	C	35M/27F	44(18);55(20)	62	52
1992	Waldhorn,RE	US	ND	P	WS,RM	C	5M/3F	47	8	5
DATA EXTRACTION - MIXED STUDIES										
NONRANDOMIZED TRIALS										
CROSSOVER - WITHIN SUBJECTS - REPEATED MEASURES DESIGN										
1995	Elliott,MW	Ldn,UK	ND	P	CSVR,WS,RM	C	11M/3F	COPD 54-71 REST 46-58	14	14
NONCROSSOVER - WITHIN SUBJECTS - BEFORE/AFTER DESIGN										
1993	Restrick,LJ	Ldn,UK	ND	P	WS,BA	C	8M/4F	57(22-71)	12	12

Age; Reported as mean(SD)
BA: Before/After
BS: Between Subjects
CSVR: Crossover

NEG: Nonequivalent Groups
RM: repeated Measures
WS: Within Subjects

Data Collection: ND - Not described
Prospective/Retrospective: P - Prospective
Sample Type: C - Convenience

M: Male
F: Female

Table 13

Bilevel NIPPV Trial Comparisons by Study Type

	RCT		NON RCT'S				OTHER		
COPD STUDIES									
Comparison	BS BA	BS RM	CSVR WS BA	CSVR WS RM	NONCSVR WS BA	NONCSVR WS RM	NEG BS BA	NEG BS RM	TOTAL NO. OF TRIALS
Bilevel vs spontaneous breathing				2					2
Bilevel vs sham NIPPV	3		1						4
Bilevel & LTOT vs LTOT		2	1	1				1	5
Bilevel & excercise vs excercise		1		1			1		3
Bilevel vs other types of ventilation				2		1		1	4
Different Bilevel pressure settings				1	1	2			4
Different types of Bilevel ventilators				2					2
Different Bilevel modes (S vs ST)									0
RESTRICTIVE STUDIES									
Comparison	RCT BS BA	RCT BS RM	NON RCT'S CSVR WS BA	NON RCT'S CSVR WS RM	NON RCT'S NONCSVR WS BA	NON RCT'S NONCSVR WS RM	OTHER NEG BS BA	OTHER NEG BS RM	TOTAL NO. OF TRIALS
Bilevel vs spontaneous breathing					2	4			6
Bilevel vs sham NIPPV									0
Bilevel & LTOT vs LTOT									0
Bilevel & excercise vs excercise						2			2
Bilevel vs other types of ventilation									0
Different Bilevel pressure settings									0
Different types of Bilevel ventilators					1				1
Different Bilevel modes (S vs ST)									0
MIXED STUDIES									
Bilevel vs other types of ventilation				1					1
Different Bilevel modes (S vs ST)					1				1

STUDY TYPES

BA: Before/After
BS: Between Subjects
CSVR: Crossover
NONCSVR: Noncrossover
NEG: Nonequivalent Groups
WS: Within Subjects
RM: Repeated Measures

Table 14
COPD Study Validity Ratings

COPD RCTs								
BETWEEN SUBJECTS - BEFORE/AFTER DESIGN								
Pub Date	First Author	Design & Allocation	Recruitment	Inclusion & Exclusion	Description of Intervention	Statistical Analysis	Outcome Measurement	Overall Validity Rating
2002	Diaz, O	HI (4/5)	HI (5/6)	HI (4/4)	HI (4/4)	HI (6/6)	MED (6/10)	HI (29/39)
1996	Gay,PC	MED (2/5)	HI (5/6)	HI (4/4)	HI (4/4)	HI (6/6)	MED (5/10)	HI (26/39)
1994	Renston,JP	HI (4/5)	MED (4/6)	MED (2/4)	HI (4/4)	HI (6/6)	LO (4/10)	MED(24/39
BETWEEN SUBJECTS - REPEATED MEASURES DESIGN								
2000	Casanova,C	HI (4/5)	HI (5/6)	HI (4/4)	HI (4/4)	HI (6/6)	HI (8/10)	HI (29/39)
2002	Clini,E	HI (4/5)	HI (5/6)	HI (4/4)	HI (4/4)	HI (6/6)	MED (7/10)	HI (31/39)
2000	Garrod,R	HI (5/5)	HI (6/6)	MED (3/4)	HI (4/4)	HI (6/6)	MED (6/10)	HI (28/39)
CROSSOVER STUDIES								
CROSSOVER - WITHIN SUBJECTS - BEFORE/AFTER DESIGN								
Pub Date	First Author	Study Design	Inclusion & Follow-up	Control of Confounders	Data Coll & Outcome Meas.	Stat Anal. & Conclusion	Discussion	Overall Validity Rating
1997	Krachman,SL	MED (3/7)	HI (4/4)	HI (3/4)	MED (4/6)	HI (5/6)	HI (2/2)	HI (21/29)
1995	Meecham Jones	MED (3/7)	HI (4/4)	HI (4/4)	MED (4/6)	HI (6/6)	MED (1/2)	HI (22/29)
CROSSOVER - WITHIN SUBJECTS - REPEATED MEASURES DESIGN								
1992	Ambrosino,N	MED (3/7)	HI (3/4)	HI (4/4)	MED (3/6)	HI (5/6)	MED (1/2)	MED
1993	Lien,TC	MED (3/7)	HI (3/4)	HI (3/4)	MED (4/6)	HI (6/6)	HI (2/2)	HI (21/29)
1996	Lin,CC	MED (4/7)	HI (5/6)	HI (4/4)	HI (4/4)	HI 5/6)	MED (5/10)	HI (22/29)
1997	Marangoni,S	MED (4/7)	HI (4/4)	HI (3/4)	MED (4/6)	HI (6/6)	HI (2/2)	HI (23/29)
1993	Nava,S	MED (4/7)	HI (3/4)	HI (3/4)	MED (3/6)	HI (6/6)	MED (1/2)	HI (20/29)
1991	Strumpf,DA	HI (6/7)	HI (4/4)	HI (4/4)	MED(4/6)	HI (6/6)	HI (2/2)	HI (22/29)
2003	Highcock,MP	MED (4/7)	HI (3/4)	HI (3/4)	MED (3/6)	HI (6/6)	HI (2/2)	HI (21/29)

HI: High MED: Medium LO: Low PUB: Publication

Table 15
COPD Study Validity Ratings

<table>
<tr><th colspan="9">COPD OBSERVATIONAL STUDIES</th></tr>
<tr><th colspan="9">NONCROSSOVER - WITHIN SUBJECTS - BEFORE/AFTER DESIGN</th></tr>
<tr><th>Publication Date</th><th>First Author</th><th>Study Design</th><th>Inclusion & Follow-up</th><th>Control of Confounders</th><th>Data Coll & Outcome</th><th>Stat Anal. & Conclusions</th><th>Discussion</th><th>Overall Validity</th></tr>
<tr><td>1993</td><td>Ambrosino,N</td><td>MED (4/7)</td><td>HI (4/4)</td><td>Hi (3/4)</td><td>MED (3/6)</td><td>HI (6/6)</td><td>HI (2/2)</td><td>HI (23/29)</td></tr>
<tr><td colspan="9">NONCROSSOVER - WITHIN SUBJECTS - REPEATED MEASURES DESIGN</td></tr>
<tr><td>1998</td><td>Bianchi,K</td><td>MED (4/7)</td><td>HI (3/4)</td><td>HI (4/4)</td><td>MED (4/6)</td><td>HI (6/6)</td><td>HI (2/2)</td><td>HI (23/29)</td></tr>
<tr><td>2002a</td><td>Vanpee,D</td><td>LO (1/7)</td><td>HI (3/4)</td><td>HI (3/4)</td><td>MED (3/6)</td><td>HI (6/6)</td><td>MED (1/2)</td><td>MED (17/29)</td></tr>
<tr><td>2000</td><td>Vitacca</td><td>HI (6/7)</td><td>HI (4/4)</td><td>HI (4/4)</td><td>HI (4/6)</td><td>HI (6/6)</td><td>HI (2/2)</td><td>HI (26/29)</td></tr>
<tr><td colspan="9"></td></tr>
<tr><td colspan="9">NONEQUIVALENT GROUPS STUDIES</td></tr>
<tr><td colspan="9">BETWEEN SUBJECTS - BEFORE/AFTER DESIGN</td></tr>
<tr><td>2001</td><td>Nava,S</td><td>MED (2/7)</td><td>HI (4/4)</td><td>HI (3/4)</td><td>MED (3/6)</td><td>HI (6/6)</td><td>MED (1/2)</td><td>HI (19/29)</td></tr>
<tr><td colspan="9"></td></tr>
<tr><td colspan="9">BETWEEN SUBJECTS - REPEATED MEASURES DESIGN</td></tr>
<tr><td>1998</td><td>Clini,E</td><td>HI (6/7)</td><td>HI (4/4)</td><td>HI (4/4)</td><td>MED (4/6)</td><td>HI (6/6)</td><td>HI (2/2)</td><td>HI (26/29)</td></tr>
<tr><td>2002b</td><td>Vanpee,D</td><td>MED (2/7)</td><td>MED (2/4)</td><td>HI (3/4)</td><td>MED (3/6)</td><td>HI (6/6)</td><td>LO (0/2)</td><td>MED (16/29)</td></tr>
</table>

HI: High MED: Medium LO: Low

Table 16
Restrictive and Mixed Study Validity Ratings

Publication Date	First Author	Study Design	Inclusion & Follow-up	Control of Confounders	Data Collection and Outcome Measurement	Statistical Analysis & Conclusions	Discussion	Overall Validity Rating
OBSERVATIONAL STUDIES								
NONCROSSOVER - WITHIN SUBJECTS - BEFORE/AFTER DESIGN								
2002	Ergun,P	MED (2/7)	HI (4/4)	MED (2/4)	MED (3/6)	HI (5/6)	MED (1/2)	MED (17/29)
2002a	Highcock,MP	MED (3/7)	HI (3/4)	HI (4/4)	MED (4/6)	HI (5/6)	MED (1/2)	HI (20/29)
1990	Strumpf,DA	MED (2/7)	MED (2/4)	HI (3/4)	LO (2/6)	LO (0/6)	LO (0/2)	LO (9/29)
NONCROSSOVER - WITHIN SUBJECTS - REPEATED MEASURES DESIGN								
1997	Fanfulla,F	MED (2/7)	HI (3/4)	HI (3/4)	MED (3/6)	HI (6/6)	MED (1/2)	HI (18/29)
2002b	Highcock,MP	MED (4/7)	HI (3/4)	HI (3/4)	MED (4/6)	HI (6/6)	HI (2/2)	HI (22/29)
1992	Hill,N	MED (3/7)	HI (4/4)	HI (4/4)	MED (4/6)	HI (5/6)	HI (2/2)	HI (22/29)
1996	Nauffal,D	MED (3/7)	HI (4/4)	HI (3/4)	MED (4/6)	HI (6/6)	HI (2/2)	HI (22/29)
1992	Waldhorn,RE	MED (2/7)	MED (2/4)	HI (3/4)	MED (3/6)	MED (4/6)	LO (0/2)	MED (14/29)
VALIDITY RATINGS - MIXED STUDIES								
CROSSOVER - WITHIN SUBJECTS - REPEATED MEASURES DESIGN								
1995	Elliott,MW	MED (4/7)	MED (2/4)	HI (3/4)	MED (3/6)	HI (5/6)	LO (0/2)	MED (17/29)
NONCROSSOVER - WITHIN SUBJECTS - BEFORE/AFTER DESIGN								
1993	Restrick,LJ	MED (3/7)	HI (3/4)	HI (4/4)	MED(4/6)	HI (5/6)	MED (1/2)	HI (20/29)

HI: High MED: Medium LO: Low

Table 17

Gas Exchange in COPD Observational Studies

COPD Noncrossover Observational Studies				
Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported for Treatment and Control Groups** *** for Statistically Significant Improvement**	**Comments**
Ambrosino 1993	3 days	WS BA	PaO_2 mmHg: **BEF** 49(7); **AFT** 55(8) 10/0; 53(8) 10/5; 59(8) 20/0,*p<0.01; 58(6) 20/5 **$PaCO_2$** mmHg: **BEF** 56(7); **AFT** 54(6) 10/0; 55(9) 10/5; 50(7) 20/0, *p<0.01; 49(9) 20/5, *p<0.01	Four 10 minute bilevel NIPPV sessions on IPAP/EPAP 10/0, 10/5, 20/0, 20/5 cmH20 Sa02% 85(7) baseline; 89(7) 10/0; 89(8) 10/5; 91(5) 20/0, *p<0.01; 92(5) on 20/5
Bianchi 1998	2 days	WS RM	**$PetCO_2$** mmHg: **Sham** 69.75(10.5); **Bilevel** 56.25(9)	PaO_2 not reported
Clini 1998	3 years	NEG BS RM	**PaO_2 mmHg**: **Rx (B)** 48.75(6.75); **3 yrs** 51(3) **CL (B)** 48(8.25); **3 yrs** 49.5(3) **$PaCO_2$ mmHg**:**Rx (B)** 52.5(4.5); **3 yrs** 51(9) **CL (B)** 51(4.5); **3 yrs** 50.25(8.25)	ABG's at baseline(B) & 1, 2, & 3 years unchanged in both the bilevel NIPPV Rx group, as well as the LTOT group
Nava 2001	4 weeks	NEG BS BA	**PaO_2 mmHg: Rx Grp BEF** 53.26(6.20); **AFT** 54.53(5.70) **CL Grp BEF** 55.77(8.38); **AFT** 55.49(7.13); **$PaCO_2$ mmHg**: **Rx Grp BEF** 56.73(6.48); **AFT** 53.78(6.64) **CL Grp BEF** 59.32(8.27); **AFT** 58.43(6.75)	$PaCO_2$ in 8 out of 13 bilevel NIPPV subjects (responders) decreased significantly from 56.73(6.48) to 51.85(4.96) mmHg *p<0.01
Vitacca 2000	1 day	WS RM	**PaO_2** mmHg: **BEF** 49.7(5.5); **U** 55.1(7.7); **P** 54.6(7.5) **$PaCO_2$** mmHg: **BEF** 58.3(7); **U** 53(6.1); **P** 53(6.1)	Assessed subjects on their 'usual' (U) & physiological' (P) NIPPV settings, which were similar: IPAP/EPAP U = 13-19/2-5; P = 12-18/2-5

Results: reported as mean(SD)

AFT: after BEF: before CL: control Rx: treatment U: Usual Bilevel NIPPV ventilator sattings P: Physiological Bilevel NIPPV settings

Table 18

Pulmonary Function (FEV1% Predicted) in COPD RCT Studies

COPD RCTs				
Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported for Treatment and Control Groups** *** for Statistically Significant Improvement**	**Comments**
Casanova 2000	1 year	BS RM	**FEV1 Liters:** **Rx** 0.84(0.25) **CL** 0.87(0.22) **FEV1 % predicted:** **Rx**: 30(9); **CL**: 31(7)	
Clini 2002	2 years	BS RM	**FEV1 % predicted:** **Rx** 12 mos 26.8(8.9); 24 mos 27.5(10.6) **CL** 12 mos 30.9(11.3); 24 mos 30.8(11.1)	Reported % predicted only
Diaz 2002	4 weeks	BS BA	**FEV1 Liters:** **Rx** 0.77(0.21) **CL** 0.79(0.21) **FEV1 % predicted:** **Rx** 35.8(11); **CL** 36.7(11)	
Garrod 2000	8 weeks	BS RM	**FEV1 Liters:** **Rx** 0.94(0.21) **CL** 0.88(0.28) **FEV1 % predicted:** **Rx** 32.5(10.7); **CL** 34.6(11)	
Gay 1996	3 months	BS BA	**FEV1 Liters:** **Rx** 0.60(0.24); **CL** 0.71(0.12)	FEV1 reported in Liters only

Results: reported as mean(SD)

AFT: after BEF: before CL: control Rx: treatment BA: Before/After BS: Between Subjects RM: Repeated Measures

Table 19
Pulmonary Function in COPD Observational Studies

COPD OBSERVATIONAL STUDIES				
Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported for Treatment and Control Groups** *** for Statistically Significant Improvement**	**Comments**
Clini 1998	3 years	NEG BS RM	**FEV1 Liters:** **Rx** 0.895(0.31) **CL** 0.85(0.30) (initial) **Rx** 0.83(0.30) **CL** 0.70(0.20) (at 3 yrs) **FEV1 % predicted:** **Rx**: 32(10); **CL**: 31(8) **Rx**: 28.7(7.8); **CL**: 27.8(6.6))	Less than expected decline in FEV1 over the 3 year period in the NIPPV grp
Lin 1996	6 weeks	CSVR RM	**FEV1 % predicted:** **Rx**: 33(6); **CL**: 33(5))	Data taken from graph;reported in % predicted only
Meecham Jones 1995	3 months	CSVR BA	**FEV1 Liters:** **Rx** 0.83(0.4); **CL** 0.81(0.4) **FEV1 % predicted:** **Rx**: 30.7(11); **CL**: 30(11)	
Nava 2001	4 weeks	BS BA	**FEV1 Liters:** **BEF** 0.69(0.25); **AFT** 0.72(0.28)	FEV1 reported in Liters only
Strumpf 1991	6 months	CSVR RM	**FEV1 Liters:** **Rx** 0.60(0.24); **CL** 0.71(0.12) **FEV1 % predicted:** **Rx** 34(2); **CL** 33(2)	

Results: reported as mean(SD)

AFT: after BEF: before CL: control Rx: treatment BA: Before/After BS: Between Subjects RM: Repeated Measures

Table 20
Ventilatory/Breathing Pattern in COPD RCT and Crossover Studies

Study ID	Length of NIPPV Trial	Study Type	Rx/CL	Mean Outcome Values - * for Significance
COPD RCT Studies				
Diaz 2002	3 weeks	BS BA	Rx CL	**VT ml**: Rx 514(173) to 694(193), *p<0.001; **VE L·min⁻¹**: 10.86(4) to 12.01(3) CL 552(147) to 543(133) 10.10(3) to 10.28(2)
			Rx CL	**Ttot s**: Rx 2.95(0.8) to 3.62(1.1), *p<0.01 CL 3.36(0.8) to 3.25(0.8)
COPD Crossover Studies				
Ambrosino 1992	2 days	CSVR RM	AFT BEF	**VT ml**: 790(98), *p<0.05 **VE L/min**: 11.1, *p<0.05 **Ttot s**: 4.5(0.8), *p<0.05 408(119) 8.2(1.8) 3.0(0.6)
			AFT BEF	**Ti s**: 1.9(0.4), *p<0.05 **Ti/Ttot %**: 43(6) **VT/Ti ml/s**: 436(148) 1.1(0.6) 37(2) 363(83)
Lien 1993	40 min	CSVR BA	AFT BEF	**VT L**: 0.35(0.15) / 350(150) ml **VT/Ti L/s**: 0.28(0.1) / 280(100) ml (Values from graph) 0.3(0.1) / 300(100) ml 0.25(0.1) / 250(100) ml
Lin 1996	6 weeks	CSVR RM	AFT BEF	**VT ml**: 251.2(33.8) **VE L**/min: 3.74(0.56) 228.2(31) 3.5(0.62)
Nava 1993	15 min x 5	CSVR RM	AFT BEF	**VT ml**: 556(242) on 10/0; 657(136) on 10/5; 766(144) on 20/0; 825(186) on 20/5 IPAP/EPAP **Baseline VT ml**: 445(76) * all VT values significant at *p<0.05
			AFT BEF	**VE L/m**: 10.5(2.0) on 10/0; 11.1(2.6) on 10/5; 11.6(2.8) on 20/0; 11.5(2.3) on 20/5 **Baseline VE L/m**: 9.6(1.5)
			AFT BEF	**Ti/Ttot %**: 38(3) on 10/0; 41(5) on 10/5; 41(3) on 20/0; 39(3) on 20/5 **Baseline Ti/Ttot**: 40(4)
			AFT BEF	**VT/Ti ml/s**: 461(70) on 10/0; 411(100) on 10/5; 474(136) on 20/0; 529(117) on 20/5 **Baseline VT/Ti ml/s**: 384(90); *p<0.05 for 10/0, 20/0 & 20/5
Highcock 2003	3 days	CSVR RM	AFT BEF	**VT ml**: (all bilevel vents)1199(371), *p<0.04; **VE L/min**: 32.7(13.8), *p<0.03; **Ti/Ttot %**: 38(4) (mouthpiece) 1035(284) 27.4(10.3) 36(4) **VT/Ti ml/s**: (all bilevel vents) 1359(485) (mouthpiece) 1210(399)

Rx: treatment group Before: BEF Ti: Inspiratory time VE: Minute ventilation VT/Ti: Mean inspiratory flow
CL: control After: AFT Ttot: Respiratory cycle VT: Tidal volume
Results: reported as mean(SD)

Table 21
Ventilatory/Breathing Pattern in COPD Observational and Restrictive Studies

Study ID	Length of NIPPV trial	Study Type	AFT BEF	Mean Outcome Values - * for Significance
				COPD Studies
				NonCrossover Observational Studies
Bianchi 1998	2 days	WS RM	BEF	**VT ml**: 1000(390) **VE L/min**: 32.3(10.2) **VT/Ti L/s**: 1.27(0.43) **Ti/Ttot%**: 44(6) (sham)
			AFT	1150(430) 34.4(13) 1.5(0.62) 39(5) (bilevel)
Nava 2001	4 weeks	NEG BS BA	BEF	**VT ml**:587.88(76.2), *p<0.01 **Ti/Ttot%**: 38(45), *p<0.01 **VTml**: 443.87(73.80); {*p<0.05
			AFT	439.07(120.17) 34(39) 387.25(114.76) {in responders
Vanpee 2002a	3 x 5 min trials	NEG BS RM	BEF	**VT ml**-Normocapnic grp: 570(250); Hypercapnic grp: 300(60)
			AFT	Normocapnic grp: 840(100), *p<0.0001; Hypercapnic grp: 700(100) on PSV 20/0,*p<0.001
			AFT	Normocapnic grp: 850(250), *p<0.01; Hypercapnic grp: 600(150) on Bilevel 20/5;*p<0.001
			AFT	Normocapnic grp: 630(100), *p<0.01; Hypercapnic grp: 360(105) on Bilevel 20/10;*p<0.001
			BEF	**VE L/min**: Normocapnic grp: 10.83(5.80) Hypercapnic grp: 5.80(1.0)
			AFT	14.99(5.58),*p<0.001; 9.17(2.80),*p<0.001 on 20/0
			BEF	**Ti/Ttot%**: Normocapnic grp: 370(60); Hypercapnic grp:300(50)
			AFT	Normocapnic grp: 420(50)*p<0.001; Hypercapnic grp: same values
Vanpee 2002b	< 1 week	WS RM	BEF	**VT ml**: 942(428) on PSV 10/0; 987(429) on PSV 15/5 during 'active breathing'
			AFT	1137(553) on PSV 10/0; 1157(486) on PSV 15/5 during 'active breathing'
				Study assessed efficacy of bilevel NIPPV during relaxed, active, and resistive breathing
Vitacca 2000	1 day	WS RM	BEF	**VT ml**: 484(184) **VE L/min**: 9.2(3.9)
			AFT	751(187) 11.7(3.9)
				Restrictive Thoracic Disease - Observational Studies
Highcock 2002b	3 days	WS RM	BEF	**Vt ml**: 476(89) **VT/Ti ml/s**: 751(277) **Ti/Ttot%**: 43(2) (for mouthpiece)
			AFT	677(156),*p=0.02; 897(283),*p=0.004; 44(30) (for all 3 bilevel vents)
Strumpf 1990	6 months	WS BA	BEF	**VT ml**: 381.4(184.37) **VE L/min**: 6.4(2.67)
			AFT	511.25(270.92) 9.3(5.27)

Results: reported as mean(SD)

Before: BEF	Ttot: Respiratory cycle	VT: Tidal volume
After: AFT	VE: Minute ventilation	VT/TI: Mean inspiratory flow

Table 22
Respiratory Muscle Function/WOB in COPD RCTs

COPD RCTs				
Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported** *** for Statistically Significant Improvement**	**Comments**
Casanova 2000	1 year	BS RM	**MIP**: **Rx** 44(15)%/ **CL** 50(19)% **MEP**: **Rx** 30(18)%/ **CL** 41(22)%	
Clini 2002	2 years	BS RM	**MIP**: **Rx** 50(20),50.7(19.7),50.6(20.6) cmH$_2$0 **MIP**: **CL** 45.7(20.9), 48.4(27.5), 48.1(27.2) cmH$_2$0	RM at 0, 12, and 24 months
Diaz 2002	3 weeks	BS BA	**PI/PImax**: **Rx** 8.7(2.2) / **CL** 12.4(3.4) cmH$_2$0 *p<0.001 **PEEPidyn**: **Rx** 1.71(0.9) / **CL** 2.69(1.2) cmH$_2$0 *p<0.001 **RL**: **Rx** 6.4(3.1) / **CL** 10.9(3.8) cmH$_2$0·L^{-1}·s^{-1} *p<0.001 **EL,dyn**: **Rx** 4.79(1.7) / **CL** 7.63(4.1) cmH$_2$0·L^{-1} *p<0.001	EL,dyn, RL, PEEPidyn, PI, TTI, PI/Pimax were all significantly decreased from baseline in the bilevel NIPPV group & not in the control
Garrod 2000	8 weeks	BS RM	**PImax**: **Rx** -60.2(19.7) to -66.6(18.2) cmH$_2$0 *p<0.05 **CL** -65.1(19.5) to -64.0(23.4) cmH$_2$0 **PEmax**: **Rx** 95.2(41.7) to 113.3(41.7) cmH$_2$0 **CL** 113.3(33.5) to 106.8(33.5) cmH$_2$0	Compared bilevel NIPPV & exercise to exercise alone
Renston 1994	2 hrs / day for 5 days	BS BA	**MIP**: **Rx** 48(19.5) / **CL** 31(19.8) cmH$_2$0 **MEP**: **Rx** 80(9.0) / **CL** 81(14.4) cmH$_2$0 **EMGdi**: 66.3(6)% reduction in Rx grp	EMGdi reported for Rx grp only

Results: reported as mean(SD)

MIP: Maximal inspiratory pressure
MEP: Maximal expiratory pressure
PI: Mean inspiratory pressure swing
PImax: Maximal inspiratory mouth pressure
PEEPidyn: Dynamic intrinsic PEEP

Pdi: Diaphragmatic pressure swings during tidal breathing
PEmax: Maximal expiratory mouth pressure
PTPdi: Pressure time product of diaphragm
TTI: Tension time index of the respiratory muscles

ELdyn: Dynamic lung elastase
EMGdi: Diaphragmatic EMG

Table 23
Respiratory Muscle Function/WOB in COPD Crossover Studies

COPD CROSSOVER STUDIES				
Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported** *** for Statistically Significant Improvement**	**Comments**
Ambrosino 1992	2 days	CSVR RM	**EMGdi** decreased in 5 out of 6 subjects during bilevel NIPPV after the first 5 minutes	Data presented on graph only
Lien 1993	40 minutes for each of 3 ventilators	CSVR RM	**PImax**: **BEF** -49.0(20.0) ; **AFT** -48.6(37.5) cmH$_2$0 **PEmax**: **BEF** 65.4(24.5) ; **AFT** 66.4(24.4) cmH$_2$0 **ΔEMGst**: -62.93(23.27)% for FEV1< 0.55L and 32.45(42.79)% for FEV1 > 0.55L, *p=0.0056	Statistically significant correlation between FEV1 of subjects and ΔEMGst r = 0.59; *p < 0.05
Lin 1996	6 weeks	CSVR RM	**MIP**: bilevel+0$_2$ 50(6.0) ; 0$_2$ 45(5) cmH$_2$0 **MEP** bilevel+0$_2$ 59(5.2) ; 0$_2$ 54(5.2) cmH$_2$0	Baseline MIP: 46.5 cmH$_2$0 Baseline MEP: 55 cmH$_2$0
Nava 1993	5 x 15 min trials	CSVR RM	**Pdi**: CL 12.87(2.83); 8.36(1.67) 10/0; *6.81(1.46) 10/5, p<0.05 7.03(1.92) 20/0; *4.96(2.35) 20/5 cmH$_2$0, p<0.01 **PEEPidyn**: CL 2.7(1.3); 2.5(1.3) 10/0; *1.05(0.7) 10/5, p<0.05; 2.6(1.0) 20/0; *0.9(0.5) 20/5 cmH$_2$0, p<0.01	Pdi and the level of PEEPi fell significantly with the addition of ipap 5 cm H$_2$0
Strumpf 1991	6 months	CSVR RM	**MIP**: **BEF** -50(6); **AFT** -47(8) cmH$_2$0 **MEP**: **BEF** 91(9); **AFT** 102(13) cmH$_2$0	

Results: reported as mean(SD)
MIP: Maximal inspiratory pressure
MEP: Maximal expiratory pressure
PI: Mean inspiratory pressure swing
PImax: Maximal inspiratory mouth pressure
PEEPidyn: Dynamic intrinsic PEEP
Pdi: Diaphragmatic pressure swings during tidal breathing
PEmax: Maximal expiratory mouth pressure
PTPdi: Pressure time product of diaphragm
TTI: Tension time index of the respiratory muscles
ELdyn: Dynamic lung elastase
EMGdi: Diaphragmatic EMG
Wdi/min: Transdiaphragmatic work
WOB/min: Inspiratory work

Table 24

Respiratory Muscle Function/WOB in COPD Observational Studies

COPD OBSERVATIONAL STUDIES				
Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported** *** for Statistically Significant Improvement**	**Comments**
Nava 2001	4 weeks	NEG BA	**Pdi:** **BEF** 7.4(3.0) ; **AFT** 6.9(3.0) cmH$_2$0 **PEEPidyn**: **BEF** 2.4(1.4) ; **AFT** 1.9(1.8) cmH$_2$0 **PTPdi/min,cmH$_2$0:BEF** 172.1(60.2) ;**AFT** 136.6(60.5), *p<0.05 **RL**: **BEF** 7.4(2.9) ; **AFT** 6.8(2.7) cmH$_2$0/l/s	Significant decrease in PTPdi/Vt ratio, Pdi and PaC0_2 became significantly decreased in 8/13 responders.
Vanpee 2002a	1 day	WS RM	Significant, incremental improvements in: **Wdi/L** and **WOB/L** with increasing IPAP and the addition of EPAP in both the normocapnic and hypercapnic COPD groups	Compared normocapnic to hypercapnic subjects with severe COPD, on bilevel NIPPV: PSV5-20/0, BP-P 10-20/5-10
Vanpee 2002b	Less than 1 week	NEG RM	**PTPdi**: RE 218(86) on 10/0; 188(86) on 15/5 cmH$_2$0 **PEEPidyn**: RE 5.6(6.0) on 10/0; 3.3(3.8) on 15/5 cmH$_2$0 **Wdi/min**: RE 16.13(8.3) on 10/0; 13.69(7.54) on 15/5 cmH$_2$0 **WOB/min**: RE 14.47(9.43) on 10/0; 11.19(8.33) on 15/5	Compared relaxed (RE), active (AC), and resisted behaviors on bilevel NIPPV 10/0 & 15/5 cm H$_2$0. Values for relaxed breathing reported here
Vitacca 2000	1 day	WS RM	**PTPdi/min**: S 347(136); U 152(116), *p< 0.01; P 126(83),*p< 0.01 **PEEPidyn**: S 3.22(2.30); *U 1.41(1.51) & *P 0.68(1.04), *p<0. 01	Compared spontaneous breathing(S) to usual(U) & physiological(P) settings

Results: reported as mean(SD)

MIP: Maximal inspiratory pressure

MEP: Maximal expiratory pressure

PI: Mean inspiratory pressure swing

PImax: Maximal inspiratory mouth pressure

PEEPidyn: Dynamic intrinsic PEEP

Pdi: Diaphragmatic pressure swings during tidal breathing

PEmax: Maximal expiratory mouth pressure

PTPdi: Pressure time product of diaphragm

TTI: Tension time index of the respiratory muscles

ELdyn: Dynamic lung elastase

EMGdi: Diaphragmatic EMG

Wdi/min: Transdiaphragmatic work

WOB/min: Inspiratory work

Table 25

Exercise Tolerance in COPD RCT and Observational Studies

Study ID	Length of NIPPV Trial	Study Type	Data Reported for Treatment and Control Groups * for Statistically Significant Improvement	Comments
COPD RCTs				
Clini 2002	2 years	BS RM	**6 MWT meters:** Rx 201(125), 202(120), 183(118) @ 0, 12, 24 mos CL 247(110), 244(108), 232(111) @ 0, 12, 24 mos	
Garrod 2000	8 weeks	BS RM	**SWT meters:** Rx 169(112) to 269(124) *p<0.001 CL 205(100) to 233(123)	Compared Bilevel NIPPV & exercise to exercise alone
Gay 1996	3 months	BS BA	**6 MWT meters:** Rx 265(153) to 312(240) CL 301(90.7) to 309.8(111)	
Renston 1994	5 days	BS BA	**6 MWT meters:** Rx 240(48) to 273(46) CL 236(30) to 234(33)	
COPD OBSERVATIONAL STUDIES				
Bianchi 1998	2 days	WS RM	**Bike Endurance time (minutes):** Rx 10.5(2.0) CL 7.2(4.4)	Endurance testing done during sham & Bilevel ventilation with an increasing load applied
Clini 1998	3 years	NEG RM	**6 MWT meters:** Rx 250(88), 291(75), 284(89) @ 1, 2, 3 years CL 229(42), 246(58), 210(42) @ 1, 2, 3 years	
Meecham J 1995	3 months	CSVR BA	**6 MWT meters:** Rx 240(100 to 450) CL 235(80 to 440)	
Nava 2001	4 weeks	NEG BA	**6 MWT meters:** Rx 299(139) to 311(107) CL 321(156) to 342(118)	
Highcock 2003	3 days	NEG RM	**SWT meters:** Rx 145(76) **Mouthpiece:** 211(96) **Unencumbered:** 259(123)	Compared 3 bilevel ventilators using nasal mask, to mouthpiece alone and unencumbered

Results: reported as mean(SD)

Treadmill: treadmill endurance   6 MWT: 6 minute walk test   SWT: shuttle walking distance

AFT: after   BEF: before   CL: control   Rx: treatment   BA: Before/After   RM: Repeated Measures   WS: Within Subjects

Table 26

Dyspnea in COPD RCT and Observational Studies

<table>
<tr><th colspan="5">COPD RCTs</th></tr>
<tr><th>Study ID</th><th>Length of NIPPV Trial</th><th>Study Type</th><th>Data Reported for Treatment and Control Groups
* for Statistically Significant Improvement</th><th>Comments</th></tr>
<tr><td>Casanova 2000</td><td>1 year</td><td>BS RM</td><td>BORG: Rx 5(1.63) CL 4(1.63)
MRC: Rx 2 CL 2</td><td></td></tr>
<tr><td>Clini 2002</td><td>2 years</td><td>BS RM</td><td>MRC: Rx 3.3(0.3), *2.7(0.8), *2.3(0.72) at 0, 12, 24 mos
CL 2.7(0.6), 3.0(0.77), 2.9(0.72) at 0, 12, 24 mos</td><td>*p = 0.048 12 mos; *p = 0.013 24 mos</td></tr>
<tr><td>Garrod 2000</td><td>8 weeks</td><td>BS RM</td><td>CRDQ Dyspnea Score: Rx 13.1 to 18 *p<0.001
CL 15.1 to 16.8</td><td>Data from the dyspnea portion of the CRDQ Instrument</td></tr>
<tr><td>Renston 1994</td><td>5 days</td><td>BS BA</td><td>BORG: Rx 2.0(1.2) to 0.7(0.9) *p<0.01
CL 1.8(1.13) to 1.3(1.13)</td><td></td></tr>
<tr><th colspan="5">COPD OBSERVATIONAL STUDIES</th></tr>
<tr><td>Bianchi 1998</td><td>2 days</td><td>WS RM</td><td>BORG: BEF: 6.3(1.4) AFT: 6.5(1.5) Sham ventilation
BEF: 6.3(1.4) AFT: 4.4(1.4) Bilevel NIPPV *</td><td>*p<0.05</td></tr>
<tr><td>Clini 1998</td><td>3 years</td><td>NEG RM</td><td>ATS: Rx BEF: 3.6(0.9) AFT: 1.8(1.7); 3.0(1.1); 3.7(1.0)
CL BEF: 3.2(1.3) AFT: 2.7(1.0); 3.0(1.1); 3.0(0.8)
VAS: Rx 23(12)% decrease;CL 16(20)% decrease</td><td rowspan="2">Dyspnea rated at 1, 2, &amp; 3 years in Bilevel NIPPV &amp; LTOT versus LTOT only</td></tr>
<tr><td>Nava 2001</td><td>4 weeks</td><td>NEG BA</td><td>VAS: BEF: 36.6(17.1) AFT: 22.8(18.3)</td></tr>
<tr><td>Strumpf 1991</td><td>6 months</td><td>WS BA</td><td>Dyspnea Scale of Mahler: BEF 0.6(1.7)
AFT 0.3(1.3)</td><td>Functional Impairment dyspnea rating</td></tr>
</table>

Results: reported as mean(SD

AFT: After
ATS-American Thoracic Society dyspnea scoring scale
BORG dyspnea scale
CRDQ-Chronic Respiratory Disease Questionnaire
Dyspnea Scale of Mahler

BEF: Before
MRCD-Medical Research Council Dyspnea Scale
MRSC-Medical Research Council Dyspnea Scale
NEG: Nonequivalent Groups
VAS: Visual Analogue Scale

BA: Before/After
BS: Between Subjects
RM: Repeated Measures
WS: Within Subjects

Table 27
Sleep in COPD Studies

Study ID	Length of NIPPV Trial	Study Type	Data Reported for Treatment and Control Groups * for Statistically Significant Improvement
COPD RCTs			
Clini 2002	2 years	BS RM	SQ: Rx 2.5(1.1), 2.0(0.9), 1.7(0.8) at 0, 12, & 24 mos CL 2.2(1.2), 2.58(1.1), 2.3(1.3) at 0, 12, & 24 mos
Garrod 2000	8 weeks	BS RM	TST%: Rx: 56.5(29 to 68) CL 42.9(25.9 to 53.4)
Gay 1996	3 months	BS BA	TST hrs: BEF Rx 4.98(0.69) CL 4.70(0.99) AFT Rx 4.59(0.69) CL 4.79(0.6) SE%: BEF Rx 71.3(5.5) CL 63.2(11.7) AFT Rx 68.3(2.5) CL 66.0(8.7)
COPD OBSERVATIONAL STUDIES			
Krachman 1997	3 nights	CSVR BA	SE%: Rx 63(7) CL 81(4) *p<0.05 TST hrs: Rx 3.42(0.53) CL 4.36(0.46) *p<0.05
Lin 1996	6 weeks	CSVR RM	SE%: Rx 60(4) CL 70(3) TST hrs: Rx 3.63(0.2) CL 4.33(0.16)
Meecham J. 1995	6 months	CSVR BA	SE%: Rx 81(5.5) CL 69(8.75) *p<0.05 TST hrs: Rx 5.65(0.66) CL 4.3(0.58) *p<0.001
Strumpf 1991	6 months	CSVR RM	SE%: Rx 53(26.46) CL 67(13.22) TST hrs: Rx 3.1(1.72) CL 4.23(1.19)

Results: reported as mean(SD

AFT: After
BA: Before/After
BEF: Before
CL: Control

CSVR: Crossover
RM: Repeated Measures
SE - Sleep Efficiency
SL - Sleep Latency

Rx: Treatment
SQ - Sleep Quality
TST - Total Sleep Time

Table 28
Functional Status/ADL in COPD Studies

COPD RCTs				
Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported for Treatment and Control Groups** *** for Statistically Significant Improvement**	**Comments**
Garrod 2000	8 weeks	BS RM	**LCADL - Total Score:** Rx 45.4 to 38.7 *$p<0.001$ CL 40.2 to 33.8 *$p<0.001$ **Physical Subscore:** Rx 6.0 to 4.65 *$p<0.001$ CL 5.75 to 5.05 *$p<0.05$ **Liesure Subscore:** Rx 7.47 to 5.82 *$p<0.001$ CL 6.25 to 5.70	Compared Bilevel NIPPV and exercise to exercise alone. No significant change in self-care or domestic score for the NIPPV group; no significant change in the leisure or self-care score for the exercise only group
Renston 1994	5 days	BS BA	**MMRCD:** Rx 3.1(0.4) to 2.6(0.5) CL 2.9(0.4) to 3.3(0.4) **Oxygen Cost Diagram:** Rx 16.6(3.7) to 17.0(4.0) CL 15.5(2.4) to 13.4(2.0) **BiPAP Functional Impairment Scale:** Rx 24.1(2.0) to 22.3(2.1) CL 24.4(1.5) to 23.5(1.9)	Three different measurement scales used to assess functional impairment with activities ofdaily living, associated with dyspnea

Results: reported as mean(SD)

BiPAP Functional Impairment Scale - Questionnaire that rates dyspnea (1 to 3 / none to severe) for each of 12 activities of daily living

LCADL - London Chest Activity of Daily Living Scale

MMRCD - Modified medical Research Council Dyspnea Scale: Rates functional impairment (0 to 4 / least to most) associated with dyspnea

Oxygen-cost Diagram - Visual analogue scale:0 = dyspnea during sleep to 40 = dyspnea walking uphill (minum score 12; maximum score 36)

Rx: Treatment	CL: Control	
BA: Before/After	BS: Between Subjects	RM: Repeated Measures

Table 29
Health - Related Quality of Life in COPD Studies

Study ID	Length of NIPPV Trial	Study Type	Data Reported for Treatment and Control Groups * for Statistically Significant Improvement	Comments
COPD RCTs				
Clini 2002	2 years	BS RM	**SGRQ:** **Rx** 66(14) **CL** 62(21) at baseline **Rx** 62.7(13.3) **CL** 59.52(20.16) at 24 mos **MRF-28:** Significant improvement in the Bilevel NIPPV group only (data in graph only; *p<0.041	Reduction in scores show trend for improvement in both groups primarily due to improvement in symptoms
Garrod 2000	8 weeks	BS RM	**CRDQ:** **Rx** 68.1(20.9) to 92.2(17.0) *p<0.001 **CL** 73.3(22.4) to 85.1(23.9) *p<0.05	CRDQ total score for Bilevel NIPPV & exercise versus exercise only groups
COPD OBSERVATIONAL STUDIES				
Meecham J. 1995	6 months	CSVR BA	**SGRQ:** **Rx** *60(26.2) p<0.001; **CL** 70(18.7)	
RESTRICTIVE OBSERVATIONAL STUDIES				
Nauffal 1996	18 months	WS RM	**SF-36:** **KYP** 78.5(37.7) *p<0.05 **NMD** 50(57.7) (Physical Role) **KYP** 79.6(30.6) *p<0.05 **NMD** 43.7(24.1) (Emotional Role) **KYP** 92.7(19) *p<0.05 **NMD** 62.5(47.8) (Social Function) Study compared kyphoscolosis (KYP) group to neuromuscular disease group (NMD) All other subscales improved for the KYP group (physical functioning, bodily pain, viatlity, mental health, & general health, but failed to do so in the NMD group.	

Results: reported as mean(SD)

CRDQ - Chronic Respiratory Disease Questionaire

MRF-28 - Maugeri Foundation Respiratory Failure Questionnaire

SF-36 - HRQOL questionnaire - 36 items, 8 categories:physical,emotional roles;physical,social functioning;pain;vitality;mental,general health/0(L)-100(H)

SGRQ - St. George's Respiratory Questionnaire: Lower score reflects improvement

BA: Before/After
CSVR: Crossover
CL: Control
BS: Between Subjects
Rx: Treatment
RM: Repeated Measures
KYP: Kyphoscoliosis
NMD: Neuromuscular Disease

Table 30
Morbidity in COPD and Restrictive Studies

Study ID	Length of NIPPV Trial	Study Type	Data Reported for Treatment and Control Groups * for Statistically Significant Improvement	Comments
			COPD RCTs	
Casanova 2000	1 year	BS RM	**Acute Exacerbations%:** Rx 52% at 3 mos; 66% at 12 mos CL 57% at 3 mos; 77% at 12 mos **Hospital Admissions%:** Rx *5% at 3 mos; 18% at 12 mos CL 15% at 3 mos; 19% at 12 mos **Intubations:** Rx 2% at 3 mos; 6% at 12 mos CL16% at 3 mos;10% at 12 mos	Greater increase in acute exacerbations in control group Number of hospital admissions significantly less in the Bilevel versus control group at 3 mos *p< 0.05; not sustained at 12 mos
Clini 2002	2 years	BS RM	**Hospital Admission Rate %Δ:** Rx 45% at 3 mos; 18% at 12 mos **ICU Admission days·patient^{-1}·year:** Rx 0.2(0.4) CL 0.4(0.8) **Hospital days/patient/year:** Rx 13.6(18.3) CL 19.3(32.9)	Hospital admission reduction in the Rx group (45%); and increase in the control group 27%)
			COPD OBSERVATIONAL STUDIES	
Clini 1998	3 years	NEG RM	**Hospital Stays days/patient/year:** Rx 37(29) to 15(12) *p < 0.001 CL 32(18) to 17(11) *p < 0.001 **ICU Admissions/patient/year:** Rx 1.0(0.7) to 0.2(0.3) *p < 0.0001 CL 1.2(0.4) to 0.9(0.3)	
			RESTRICTIVE OBSERVATIONAL STUDIES	
Nauffal 1996	18 months	WS RM	Hospitalization Rate admissions/year: 1.2(1.8) to 0.8(1.2) *p<0.01 in the kyphoscoliosis group 1.1(1.2) to 0.3(1.2) in the neuromuscular group *p = 0.005	

Results: reported as mean(SD)

BS: Between Subjects	WS: Within Subjects	Rx: Treatment
RM: Repeated Measures	NEG: Nonequivalent Groups	CL: Control

Table 31
Mortality Outcomes

Study ID	Length of NIPPV Trial	Study Type	Data Reported for Treatment and Control Groups * for Statistically Significant Improvement	Comments
COPD RCTs				
Casanova 2000	1 year	BS RM	**Mortality Rate**: **Rx** 18%; **CL** 17%	
Clini 2002	2 years	BS RM	**Mortality Rate: Rx** 16%; **CL** 13% at 1 year **Rx** 33% **CL** 28% at 2 years **Rx** 46% **CL** 50% at 3 years	No significant difference in mortality between the 2 groups
COPD OBSERVATIONAL STUDIES				
Clini 1998	3 years	NEG BS RM	**Mortality Rate:** No significant difference between Rx and CL groups. Data displayed in Kaplan Meier survuval curves.	

Results: reported as mean(SD)

Rx: treatment
CL: Control
BS: Between subjects
NEG: Nonequivalent Groups
RM: Repeated Measures

Table 32
Comfort/Compliance Issues

Study ID	No.of Patients Non-compliant	Reason(s) For Noncompliance Reported	Comments
COPD RCTs			
Casanova 2000	5 out of 26	NIPPV pressure too high	Mean I/E was 12/2 cmH20
Clini 2002	3 out of 39	Lack of compliance to ventilator with no other reason given	Compliance increased with prolonged use
Garrod 2000	2 out of 23	Dry nose, mouth;disturbance to spouse;inability ot sleep due to ventilator noise	4 wk acclim; 8wks NIPPV; IPAP 13-24; EPAP 4-6 cmH20
Gay 1996	3 out of 7	Inability to sleep due to mask discomfort	1.5 days acclim; 3 mos NIPPV; I/E 10/2
Renston 1994	3 out of 7	Inability to sleep	No acclim; 2h x 5 days NIPPV; I/E 15-20/2
COPD OBSERVATIONAL STUDIES			
Ambrosino 1992	1 out of 8	Intolerance to NIPPV due to severe degree of hyperinflation	2 day study; no acclimatization; I/E 22/0
Ambrosino 1993	2 out of 9	2 patients did not tolerate addition of EPAP due to sense of discomfort during exhalation	3 days NIPPV; 2 wk acclim; I/E 10&20/0&5 didn't tolerate addition of EPAP 5 cmH20
Clini 1998	28 out of 49	28/49 NIPPV patients voluntarily became controls due to refusal or noncompliance. included nasal skin lesions (6/28), gastric distension (4/28), rhinnorrhea (4/28), mucosal dryness (2/28), skin inflammation (1/28), and none (11/28).	2 nights acclimatization; 3 year study; IPAP 10 to 16 & EPAP 2 to 4 cmH20
Lin 1996	2 out of 12	Mask intolerance and asynchronous breathing during sleep	No acclim; 6 wks NIPPV; I/E 8-15/<2
Meecham J 1995	1 out of 18	Ventilator intolerance; reasons not clearly stated	2 nite acclim; 3 mos NIPPV; I/E 16-22/2-4
Nava 1993	1 out of 7	Unable to tolerate higher pressures/IPAP of 20	One day NIPPV; Tolerated I/E 10/0 and 10/5
Nava 2001	1 out of 14	Reported side effects included leaks, nose abrasions, difficulty with head gear	2 hrs acclim; 4 wks NIPPV; max tolerated IPAP/ EPAP no > 4 cmH20
Strumpf 1991	7 out of 19	Nasal mucosal irritation unresponsive to nasal corticosteroids or humidification; inability to sleep on bilevel NIPPV; excessive anxiety with use	2 to 3 hrs acclim; 6 mos NIPPV; 15(1)/2
Vanpee 2002	3 out of 10	Asynchronous behavior	No acclim; < 1 wk NIPPV; 15/5

I/E: IPAP/EPAP cmH20 Acclim: acclimatization

Table 33
Gas Exchange in Restrictive Studies

Restrictive Oservational Studies				
Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported for Treatment and Control Groups** *** for Statistically Significant Improvement**	**Comments**
Ergun 2002	15 days	WS BA	**Pa0$_2$** mmHg: **BEF** 65(16.6); **AFT** 72.75(13.86) **PaC0$_2$** mmHg: **BEF** 45.35(10.54); **AFT** 38.5(9.24)	15 days of bilevel NIPPV for 2 hours/day
Fanfulla 1997	2 years	WS RM	**Pa0$_2$** mmHg: **BEF** 78.0(6.1); **AFT** 81.7(5.81) **PaC0$_2$** mmHg: **BEF** 44.3(2.97); **AFT** 45.5(4.5)	%Time in bed Sa0$_2$<90%: decreased from 22.8(16.6-32.0)% to 0.6(0.1-0.2)%
Highcock 2002a	3 days	WS BA	**Sa0$_2$%**: Q 92.5(2.6); V 92.8(2.1) ; **PtC0$_2$**mmHg: Q 54.75(9.75); V 53.25(9.0)	Compared 2 bilevel vents: Quantum (Q) &VPAP (V)
Hill 1992	3 weeks	WS RM	**Pa0$_2$** mmHg: **B** 76(6); **W** 69(7); **R** 74(6) **PaC0$_2$** mmHg: **B** 54(5); **W** 56(5); **R** 54(5)	Baseline (B), without bilevel NIPPV for 1 week (W), and after resumption (R)
Nauffal 1996	18 months	WS RM	Kyphoscoliosis **PaO$_2$** mmHg: **B** 57.5(8.1); 18m 64.4(10.8) **PaC0$_2$** mmHg: **B** 56.8(12.6); 18m 46(6.1),*p<0.05	Assessed Pa0$_2$, PaC0$_2$, & time Sa0$_2$ <90% baseline(B), 3, 6, 9,12, &18 months in subjects with kyphoscoliosis and neuromuscular disease; Baseline & 18 month values reported
			Neuromuscular disease **Pa0$_2$**: **B** 70.6(15.7); 18m 73.8(15.1) **PaC0$_2$**: **B** 51.3(11.9); 18m 47(9.2)	
			% of night Sa0$_2$<90%: decreased from 42(36.7) to 12.5(27.4) & from 26.8(36) to 7.1(21) in kyph & NMD groups	
Strumpf 1990	2 weeks to 5 mos	WS BA	**Pa0$_2$** mmHg: **BEF** 69.3(16.65); **AFT** 92.3(11.37) **PaC0$_2$** mmHg: **BEF** 62.3(11.85); **AFT** 43.3(1.2)	Mean values for 4 subjects on bilevel NIPPV from 2 weeks to 5 months
Waldhorn 1992	3 months	WS RM	**Pa0$_2$**mmHg Awake: **BEF** 74(27.04); **AFT** 67(11.46) Asleep: **BEF** 63.6(32.92); **AFT** 78.2(19) **PaC0$_2$**mmHg Awake: **BEF** 57.2(9.47); **AFT** 48.75(9.65) Asleep: **BEF** 66.2(11.58); **AFT** 50.2(8.04)	Compared gas exchange awake and asleep at baseline (BEF) and after 3 months of bilevel NIPPV (AFT) Data excluded for obesity hypoventilation

Results: reported as mean(SD)

AFT: after BEF: before BA: Before/After WS: Within Subjects RM: Repeated Measures

B; Baseline

Table 34
Pulmonary Function in Restrictive Studies

RESTRICTIVE OBSERVATIONAL STUDIES				
Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported for Treatment and Control Groups * for Statistically Significant Improvement**	**Comments**
Ergun 2002	15 days	WS BA	**FVC % Predicted**: **BEF 34.85** **AFT *51(16.19)**	FVC reported as % predicted only Improvement in FVC significant; $p < 0.01$
Fanfulla 1997	2 years	WS RM	**VC Liters**: **BEF** 7.52(1.3) **AFT** 5.94(2.8-10.9)	
Hill 1992	3 weeks	WS RM	**FVC Liters**: **BEF** 0.95(2.09) **AFT** 1.01(2.17) **FVC % Predicted**: **BEF** 24.66 **AFT** 26.03(13.7)	
Nauffal 1996	18 months	WS RM	**FVC % Predicted**: **BEF** 42.2(19); **6mos** 46.3(16.5); (kyphoscoliosis) **12mos** 4.1915.5); **18mos** 45.0(17.2) (NMD) **BEF** 37.5(20.3); **6mos** 35.5(18.4) **12mos** 27.8(21.6); **18mos** 24(15.2)	Compared subjects with kyphoscoliosis (KY) to those with neuromuscular disease (NMD)

Results: reported as mean(SD)

AFT: after BEF: before CL: control Rx: treatment BA: Before/After RM: Repeated Measures WS: Within Subjects

Table 35
Respiratory Muscle Function/WOB in Restrictive Studies

RESTRICTIVE OBSERVATIONAL STUDIES				
Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported** *** for Statistically Significant Improvement**	**Comments**
Ergun 2002	15 days	WS BA	**EMGdi** in 4/12 patients: **BEF** 198.91(137.13); **AFT** 174.90(75.93) µV	
Hill 1992	3 weeks	WS RM	**PImax**: **B** -32(6); **WO** -33(5); **RE** -29(3) cmH$_2$0 **PEmax**: **B** 66(10); **WO** 64(11); **RE** 63(10) cmH$_2$0	Baseline(B), without(WO) bilevel for 8(2) days & resumption(RE)
Nauffal 1996	18 months	WS RM	**Kyphoscoliosis MIP**: **B** 58(17); **3m** 60(17.1); **6m** 59.4(11.6); **9m** 61.3(13.7); **12m** 62.1(17.3); **18m** 62.4(18.1) % predicted **Neuromuscular disease MIP**: **B** 41.5(16.8); **3m** 41(13.5); **6m** 43.8(23.5); **9m** 42.1(24.4); **12m** 39.1(25.1); **18m** 35.1(26.9) % predicted	Assessed MIP % predicted at baseline(B), 3, 6, 9,12, and 18 subjects with kyphoscoliosis and neuromuscular disease

Results: reported as mean(SD)

EMGdi: Diaphragmatic EMG

MIP: Maximal inspiratory pressure

MEP: Maximal expiratory pressure

PEmax: Maximal expiratory mouth pressure

PImax: Maximal inspiratory mouth pressure

Table 36

Exercise Tolerance in Restrictive Studies

Study ID	Length of NIPPV Trial	Study Type	Data Reported for Treatment and Control Groups * for Statistically Significant Improvement	Comments
			RESTRICTIVE OBSERVATIONAL STUDIES	
Ergun 2002	15 days	WS BA	**6 MWT meters: BEF**: 320.41(93.56) **AFT**: 382.41(121.20) *p<0.05	
Highcock 2002b	3 days	WS RM	**SWT meters: Rx** 145(76) **Mouthpiece**: 140.4(75.8) **Unencumbered**: 203.7(134.9)	Compared 3 bilevel ventilators using nasal mask, to mouthpiece alone and unencumbered

Results: reported as mean(SD)

Treadmill: treadmill endurance

AFT: after BEF: before

6 MWT: 6 minute walk test

CL: control Rx: treatment

SWT: shuttle walking distance

BA: Before/After RM: Repeated Measures WS: Within Subjects

Table 37

Dyspnea in Restrictive Studies

RESTRICTIVE OBSERVATIONAL STUDIES				
Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported for Treatment and Control Groups** *** for Statistically Significant Improvement**	**Comments**
Ergun 2002	15 days	WS BA	**ATS**: **BEF** 2.5(0.9) **AFT** 1.6(0.4)	
Hill 1992	3 weeks	WS RM	**VAS**: **BEF** 3.1(1.46) **AFT** Without Bilevel 5.0(1.95) **AFT** Resumed Bilevel 2.7(1.2)	Initial rating, after withdrawal of Bilevel for 8(2) days, & after Bilevel resumed
Nauffal 1996	18 months	WS RM	**BORG**: **BEF** 4.5(1.2) **AFT** *3.5(2.2),*3(1.2),*3.4(2.2),*3.8(1.3),*3.1(1.2) at 3, 6, 9, 12, & 18 mos in kyphoscoliosis grp	Dyspnea rated in kyphoscoliosis & neuromuscular disease groups *p<0.05 versus baseline
			BEF 2.7(1.9) **AFT** 2.34(1.8, 2.7(1.5), 2.8(1.2), 3.2(2), & 3.3(3.1) at 3, 6, 9, 12, & 18 mos in neuromuscular grp	
Waldhorn 1992	3 months	WS RM	Patients reported significant improvement in daytime dyspnea. No actual data provided in the study	It was not identified how dyspnea was measured

Results: reported as mean(SD)

ATS-American Thoracic Society dyspnea scoring scale

BA: Before/After

BORG dyspnea scale

CRDQ-Chronic Respiratory Disease Questionnaire

Dyspnea Scale of Mahler

MMRCD: Medical Research Council Dyspnea Scale

MRSC-Medical Research Council Dyspnea Scale

VAS-Visual Analog Scale

RM: Repeated Measures

WS: Within Subjects

Table 38
Sleep Outcomes in Restrictive and Mixed Studies

Study ID	Length of NIPPV Trial	Study Type	Data Reported for Treatment and Control Groups * for Statistically Significant Improvement	Comments
RESTRICTIVE STUDIES				
Highcock 2002a	3 days	WS BA	**SE%:** **QPSV** 73.1(17.4) **VPAP** 79.8(10.1) **TST hrs**: **QPSV** 5.05(1.32) **VPAP** 5.24(0.9)	Compared 2 bilevel ventilators: Quantum PSV (QPSV) & Sullivan VPAP (VPAP)
Hill 1992	3 weeks	WS RM	**TST hrs**: **Initial** 7.5(0.3) **Without** 5.6(0.8)*$p<0.05$ **With** 7.5(0.3) **SS:** **Initial** 2.0(0.5) **Without** 3.9(0.8)*$p<0.05$ **With** 2.0(0.5)	Measured outcomes in response to a period of withdrawal of Bilevel NIPPV
MIXED STUDIES				
Elliott 1995	2 nights	CSVR WS RM	**TST hrs: IPAP** 3.8(2.0) **IPAP/EPAP** 4.2(1.25) (COPD group) **IPAP** 5.35(0.71) **IPAP/EPAP** 4.6(1.21) (Kyph group)	Study included COPD and kyphoscoliosis cohorts
Restrick 1993	3 nights	WS BA	No separate data for the COPD versus Restrictive Thoracic Lung group	

Results: reported as mean(SD)

BA: Before/After
CSVR: Crossover
RM: Repeated Measures
SE - Sleep Efficiency
SL: Sleep Latency
SS: Sleepiness Score
SQ - Sleep Quality
TST - Total Sleep Time
WS: Within Subjects

Table 39
Symptom Relief

Study ID	Length of NIPPV Trial	Study Type	Data Reported for Treatment and Control Groups * for Statistically Significant Improvement	Comments
COPD OBSERVATIONAL STUDIES				
Meecham J. 1995	6 months	CSVR BA	**Symptom score**: on the SGRQ health related quality of life instrument showed a significantly better symptom score for the Bilevel NIPPV group; *p = 0.007 compared to the run-in period, and *p = 0.03 compared to the oxygen alone period	
RESTRICTIVE OBSERVATIONAL STUDIES				
Fanfulla 1997	2 years	WS RM	**Questionnaire**: No scores provided; Study stated that there was resolution of symptoms of daytime sleep disordered breathing with the use of Bilevel NIPPV, which was associated with normalization of nocturnal Sa02	Used a questionnaire to assess symptoms related to sleep disturbance (daytime sleepiness or fatigue, loss of concentration during daily activities
Hill 1992	3 weeks	WS RM	**Symptom Scores: With (W); without (WO); after resumption (R)of NIPPV** **Dyspnea:** **W** 3.1(0.6) **WO** 5.0(0.8) *p<0.05 **R** 2.7(0.5) **Energy:** **W** 7.0(0.7) **WO** 4.3(0.4) *p<0.05 **R** 7.2(0.5) **Sleepiness:** **W** 2.0(0.5) **WO** 3.9(0.8) *p<0.05 **R** 2.0(0.5) **Days feeling rested in AM:** **W** 6.5(0.5) **WO** 1.2(0.7) *p<0.05 **R** 6.5(0.5) **AM headache:** **W** 0.3(0.2) **WO** 4.8(1.1) *p<0.05 **R** 0.2(0.2)	
Waldhorn 1992	3 months	WS RM	Patients reported significant improvement in daytime dyspnea. No actual data provided in the study	It was not identified how dyspnea was measured

Results: reported as mean(SD)
BA: Before/After
CSVR: Crossover
RM: Repeated Measures

SGRQ: St.George,s Respiratory Questionnaire
WS: Within Subjects

R: Resumption
W: With
WO: Without

Table 40
Gas Exchange in Mixed Studies

Study ID	**Length of NIPPV Trial**	**Study Type**	**Data Reported for Treatment and Control Groups** *** for Statistically Significant Improvement**	**Comments**
			Mixed Observational Studies	
Restrick 1993	3 nights	WS BA	**Sa0$_2$%**: COPD **B** 86.3(8.14); **S** 89.92(4.5); **ST** 89.86(5.84) REST **B** 88.1(4.8); **S** 93.1(2.5); **ST** 92.6(2.79)	Assessed Sa0$_2$ and PtC0$_2$ at baseline (B), on S mode , and on ST mode in COPD and restrictive (REST) thoracic lung disorders
			PtC0$_2$mmHg:COPD **B** 61.3(8.2); **S** 58.5(12.12); **ST** 58.65(9.2) REST **B** 54.3(3.9); **S** 51.2(4.85); **ST** 53.03(4.78)	
Elliott 1995	2 nights	CSVR WS RM	**Sa0$_2$%**: COPD **IPAP** 85.7(4.6); **IPAP/EPAP** 85.4(5.9) REST **IPAP** 93.7(1.5); **IPAP/EPAP** 93.1(0.9)	Mean nocturnal Sa0$_2$
			Sa0$_2$min: COPD **IPAP** 67.7(16.2); **IPAP/EPAP** 65.6(19.3) REST **IPAP** 77.1(6.7) **IPAP/EPAP** * 83.6(4.2) **PtC0$_2$**mmHg:COPD **IPAP** 61.3(8.2); **IPAP/EPAP** 58.65(9.2) REST **IPAP** 53.25(6.75); **IPAP/EPAP** 51.75(6.75)	Significant increase in minimum nocturnal Sa0$_2$ *p=0.02, and decrease in PtC0$_2$max *p=0.04, in the restrictive group with the addition of EPAPin restrictive subjects

Results: reported as mean(SD)

B: Baseline REST: Restrictive thoracic lung disease S: On S Bilevel mode ST: On ST Bilevel mode

Figure 1
Combined analysis for Pa02 in COPD RCTs

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 01 RCT Trials of Bilevel NIPPV versus all modalities (LTOT, Sham ventilation, Excercise)
Outcome: 01 PO2 cm H20

Study or sub-category	N	Bilevel Mean (SD)	N	Control Mean (SD)	Weight %	WMD (random) 95% CI
Casanova 2000	20	56.30(8.20)	24	57.30(6.50)	24.80	-1.00 [-5.44, 3.44]
Clini 2002	23	69.00(8.25)	24	65.00(6.00)	27.69	4.00 [-0.14, 8.14]
Diaz 2002	18	53.77(7.95)	18	50.47(6.00)	23.37	3.30 [-1.30, 7.90]
Garrod 2000	17	66.10(8.55)	20	66.80(9.38)	15.86	-0.70 [-6.48, 5.08]
Gay 1996	4	70.50(4.70)	6	60.30(14.40)	3.81	10.20 [-2.21, 22.61]
Renston 1994	9	66.00(15.00)	8	67.00(8.48)	4.47	-1.00 [-12.43, 10.43]
Total (95% CI)	91		100		100.00	1.86 [-0.60, 4.32]

Test for heterogeneity: Chi² = 5.73, df = 5 (P = 0.33), I² = 12.7%
Test for overall effect: Z = 1.49 (P = 0.14)

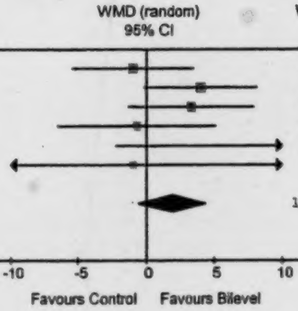


Figure 2
Combined Analysis for PaC02 in COPD RCTs

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 01 RCT Trials of Bilevel NIPPV versus all modalities (LTOT, Sham ventilation, Excercise)
Outcome: 02 PCO2 cm H20

Study or sub-category	N	Bilevel Mean (SD)	N	Control Mean (SD)	Weight %	WMD (random) 95% CI
Casanova 2000	20	51.10(8.80)	24	52.30(6.10)	18.77	-1.20 [-5.76, 3.36]
Clini 2002	23	54.00(5.62)	24	59.00(4.87)	22.05	-5.00 [-8.01, -1.99]
Diaz 2002	18	48.37(3.97)	18	54.37(6.00)	21.42	-6.00 [-9.32, -2.68]
Garrod 2000	17	43.30(6.68)	20	44.20(9.07)	17.64	-0.90 [-5.99, 4.19]
Gay 1996	4	57.50(14.40)	6	50.20(4.30)	5.50	7.30 [-7.23, 21.83]
Renston 1994	9	52.00(9.00)	8	44.00(4.24)	14.62	8.00 [1.43, 14.57]
Total (95% CI)	91		100		100.00	-1.20 [-5.05, 2.65]

Test for heterogeneity: Chi² = 18.76, df = 5 (P = 0.002), I² = 73.3%
Test for overall effect: Z = 0.61 (P = 0.54)

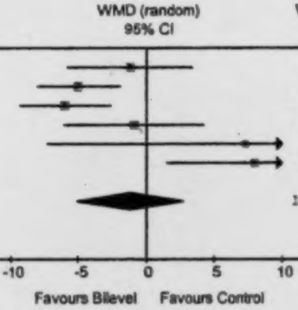


Figure 3
Combined Analysis for Pa02 in COPD Crossover Trials

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 01 P02 mmHg

Study or sub-category	Favours Bilevel N	Favours Control N	mean difference (SE)	Weight %	mean difference (random) 95% CI
Ambrosino 1992	7	7	5.0000 (2.4201)	18.22	5.00 [0.26, 9.74]
Krachman 1997	6	6	3.6500 (10.0177)	2.26	3.65 [-15.98, 23.28]
Lin 1996	10	12	0.3000 (1.3508)	26.08	0.30 [-2.35, 2.95]
Marangoni 1997	14	14	13.2000 (4.3177)	9.32	13.20 [4.74, 21.66]
Meecham Jones 1995	14	14	5.9000 (2.7030)	16.44	5.90 [0.60, 11.20]
Nava 1993	6	7	5.1000 (1.9522)	21.51	5.10 [1.27, 8.93]
Strumpf 1991	7	7	2.0000 (5.6552)	6.17	2.00 [-9.08, 13.08]
Total (95% CI)	64	67		100.00	4.49 [1.43, 7.55]

Test for heterogeneity: $Chi^2 = 12.51$, df = 6 (P = 0.05), $I^2 = 52.0\%$
Test for overall effect: Z = 2.88 (P = 0.004)

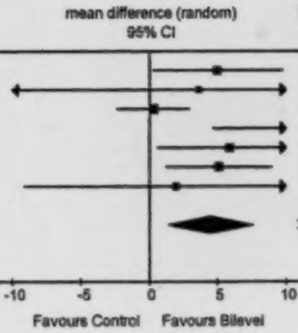


Figure 4
Combined Analysis for PaC02 in COPD Crossover Trials

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 02 PC02 cmH20 / *ETC02 cmH20

Study or sub-category	Favours Bilevel N	Favours Control N	Mean difference (SE)	Weight %	Mean difference (random) 95% CI
Ambrosino 1992	7	7	-7.0000 (3.2071)	10.46	-7.00 [-13.29, -0.71]
Krachman 1997	6	6	-3.2700 (3.9438)	7.67	-3.27 [-11.00, 4.46]
Lien 1993	11	11	-0.8000 (4.9179)	5.33	-0.80 [-10.44, 8.84]
Lin 1996	10	12	-0.9000 (1.4299)	24.29	-0.90 [-3.70, 1.90]
Marangoni 1997	14	14	-6.0000 (2.8885)	12.08	-6.00 [-11.66, -0.34]
Meecham Jones 1995	14	14	-4.5000 (1.9744)	18.72	-4.50 [-8.37, -0.63]
Nava 1993	6	7	-7.7000 (2.7889)	12.65	-7.70 [-13.17, -2.23]
Strumpf 1991	7	7	3.0000 (3.6061)	8.80	3.00 [-4.07, 10.07]
Total (95% CI)	75	78		100.00	-3.52 [-5.93, -1.11]

Test for heterogeneity: $Chi^2 = 11.16$, df = 7 (P = 0.13), $I^2 = 37.3\%$
Test for overall effect: Z = 2.86 (P = 0.004)

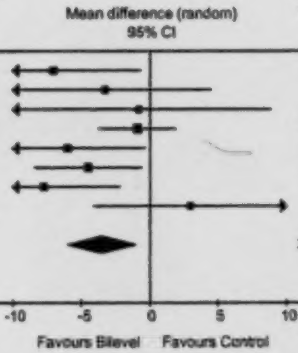
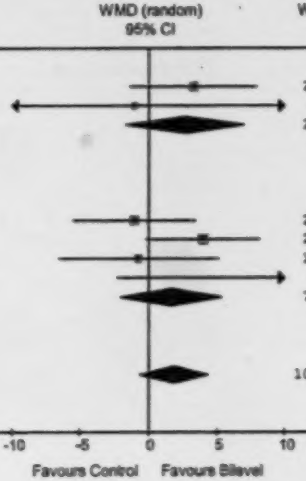


Figure 5
Combined Analysis for Pa02 in RCTs by Length of Bilevel NIPPV Trial

Review:	A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison:	02 RCT Trials of Bilevel NIPPV versus all modalities (by length of trial)
Outcome:	01 P02 cm H20



Study or sub-category	N	Bilevel Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
01 Studies 8 weeks or less							
Diaz 2002	18	53.77(7.95)	18	50.47(6.00)		23.37	3.30 [-1.30, 7.90]
Renston 1994	9	66.00(15.00)	8	67.00(8.48)		4.47	-1.00 [-12.43, 10.43]
Subtotal (95% CI)	27		26			27.84	2.70 [-1.57, 6.97]
Test for heterogeneity: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%							
Test for overall effect: Z = 1.24 (P = 0.22)							
02 Studies longer than 8 weeks							
Casanova 2000	20	56.30(8.20)	24	57.30(6.50)		24.80	-1.00 [-5.44, 3.44]
Clini 2002	23	69.00(8.25)	24	65.00(6.00)		27.69	4.00 [-0.14, 8.14]
Garrod 2000	17	66.10(8.55)	20	66.80(9.38)		15.86	-0.70 [-6.48, 5.08]
Gay 1996	4	70.50(4.70)	6	60.30(14.40)		3.81	10.20 [-2.21, 22.61]
Subtotal (95% CI)	64		74			72.16	1.68 [-1.98, 5.34]
Test for heterogeneity: Chi² = 5.06, df = 3 (P = 0.17), I² = 40.8%							
Test for overall effect: Z = 0.90 (P = 0.37)							
Total (95% CI)	91		100			100.00	1.86 [-0.60, 4.32]
Test for heterogeneity: Chi² = 5.73, df = 5 (P = 0.33), I² = 12.7%							
Test for overall effect: Z = 1.49 (P = 0.14)							

Figure 6
Combined Analysis for PaC02 in RCTs by Length of Bilevel NIPPV Trial

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 02 RCT Trials of Bilevel NIPPV versus all modalities (by length of trial)
Outcome: 02 PC02 cm H20

Study or sub-category	N	Bilevel Mean (SD)	N	Control Mean (SD)	Weight %	WMD (random) 95% CI
01 Studies 8 weeks or less						
Diaz 2002	18	48.37(3.97)	18	54.37(6.00)	21.42	-6.00 [-9.32, -2.68]
Renston 1994	9	52.00(9.00)	8	44.00(4.24)	14.62	8.00 [1.43, 14.57]
Subtotal (95% CI)	27		26		36.04	0.70 [-13.01, 14.41]
Test for heterogeneity: Chi² = 13.88, df = 1 (P = 0.0002), I² = 92.8%						
Test for overall effect: Z = 0.10 (P = 0.92)						
02 Studies longer than 8 weeks						
Casanova 2000	20	51.10(8.80)	24	52.30(6.10)	18.77	-1.20 [-5.76, 3.36]
Clini 2002	23	54.00(5.62)	24	59.00(4.87)	22.05	-5.00 [-8.01, -1.99]
Garrod 2000	17	43.30(6.68)	20	44.20(9.07)	17.64	-0.90 [-5.99, 4.19]
Gay 1996	4	57.50(14.40)	6	50.20(4.30)	5.50	7.30 [-7.23, 21.83]
Subtotal (95% CI)	64		74		63.96	-2.34 [-5.55, 0.87]
Test for heterogeneity: Chi² = 4.88, df = 3 (P = 0.18), I² = 38.5%						
Test for overall effect: Z = 1.43 (P = 0.15)						
Total (95% CI)	91		100		100.00	-1.20 [-5.05, 2.65]
Test for heterogeneity: Chi² = 18.76, df = 5 (P = 0.002), I² = 73.3%						
Test for overall effect: Z = 0.61 (P = 0.54)						

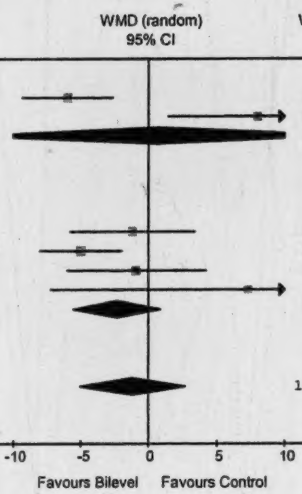


Figure 7
Combined Analysis for FEV1% Predicted in COPD RCTs

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 01 RCT Trials of Bilevel NIPPV versus all modalities (LTOT, Sham ventilation, Excercise)
Outcome: 03 FEV1 % Predicted

Study or sub-category	Bilevel N	Bilevel Mean (SD)	Control N	Control Mean (SD)	Weight %	WMD (random) 95% CI
Casanova 2000	20	30.00(9.00)	24	31.00(7.00)	33.05	-1.00 [-5.84, 3.84]
Clini 2002	39	27.50(10.60)	46	30.80(11.10)	36.22	-3.30 [-7.92, 1.32]
Diaz 2002	18	35.80(11.00)	18	36.70(11.00)	14.98	-0.90 [-8.09, 6.29]
Garrod 2000	17	32.50(10.70)	20	34.60(11.00)	15.75	-2.10 [-9.11, 4.91]
Total (95% CI)	94		108		100.00	-1.99 [-4.77, 0.79]

Test for heterogeneity: Chi² = 0.56, df = 3 (P = 0.91), I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)

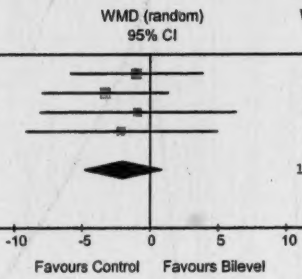
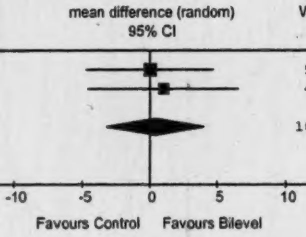


Figure 8
Combined Analysis for FEV1% Predicted in Crossover Trials

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 12 Pulmonary Function (FEV1 % Predicted)

Study or sub-category	Favours Bilevel N	Favours Control N	mean difference (SE)	Weight %	mean difference (random) 95% CI
Lin 1996	10	12	0.0000 (2.3839)	58.45	0.00 [-4.67, 4.67]
Strumpf 1991	7	7	1.0000 (2.8276)	41.55	1.00 [-4.54, 6.54]
Total (95% CI)	17	19		100.00	0.42 [-3.16, 3.99]

Test for heterogeneity: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)



Ventilatory/Breathing Pattern in COPD Crossover Studies

Figure 9
Combined Analysis for Tidal Volume (VT ml) on COPD Crossover Trials

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 05 Tidal Volume (VT ml)

Study or sub-category	Favours Bilevel N	Favours Control N	mean difference (SE)	Weight %	mean difference (random) 95% CI
Ambrosino 1992	7	7	382.0000 (58.2666)	21.59	382.00 [267.80, 496.20]
Highcock 2003	8	8	164.0000 (165.1882)	13.03	164.00 [-159.76, 487.76]
Lien 1993	11	11	50.0000 (54.3557)	21.86	50.00 [-56.54, 156.54]
Lin 1996	10	12	23.0000 (13.9401)	23.68	23.00 [-4.32, 50.32]
Nava 1993	6	7	380.0000 (81.1858)	19.85	380.00 [220.88, 539.12]
Total (95% CI)	42	45		100.00	195.64 [21.97, 369.31]

Test for heterogeneity: Chi^2 = 53.19, df = 4 (P < 0.00001), I^2 = 92.5%
Test for overall effect: Z = 2.21 (P = 0.03)

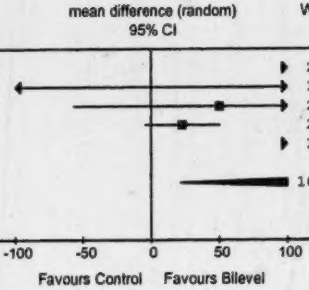
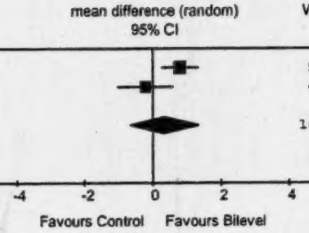


Figure 10
Combined Analysis for Inspiratory Time (Ti ml) on COPD Crossover Trials

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 06 Inspiratory Time (Ti sec)

Study or sub-category	Favours Bilevel N	Favours Control N	mean difference (SE)	Weight %	mean difference (random) 95% CI
Ambrosino 1992	7	7	0.8000 (0.2725)	54.45	0.80 [0.27, 1.33]
Nava 1993	6	7	-0.2200 (0.4085)	45.55	-0.22 [-1.02, 0.58]
Total (95% CI)	13	14		100.00	0.34 [-0.66, 1.33]

Test for heterogeneity: Chi^2 = 4.31, df = 1 (P = 0.04), I^2 = 76.8%
Test for overall effect: Z = 0.66 (P = 0.51)



Ventilatory/Breathing Pattern in COPD Crossover Studies

Figure 11
Combined Analysis for Mean Inspiratory Flow (VT/Ti ml/sec) on COPD Crossover Trials

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 07 Mean Inspiratory Flow (VT/Ti ml/sec)

Study or sub-category	Favours Bilevel N	Favours Control N	mean difference (SE)	mean difference (random) 95% CI	Weight %	mean difference (random) 95% CI
Ambrosino 1992	7	7	73.0000 (64.1349)		22.02	73.00 [-52.70, 198.70]
Highcock 2003	8	8	149.0000 (222.0434)		1.84	149.00 [-286.20, 584.20]
Lien 1993	11	11	30.0000 (42.6401)		49.81	30.00 [-53.57, 113.57]
Nava 1993	6	7	145.0000 (58.6399)		26.34	145.00 [30.07, 259.93]
Total (95% CI)	32	33			100.00	71.94 [12.96, 130.92]

Test for heterogeneity: Chi² = 2.64, df = 3 (P = 0.45), I² = 0%
Test for overall effect: Z = 2.39 (P = 0.02)

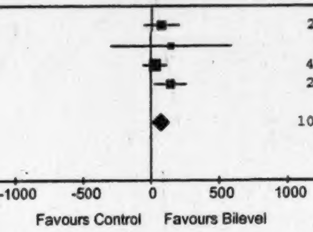
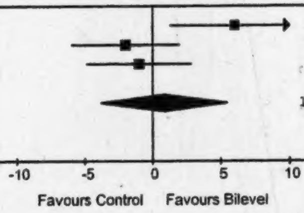


Figure 12
Combined Analysis for Respiratory Duty Cycle (Ti/Ttot%) on COPD Crossover Trials

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 09 Ti/Ttot Ratio %

Study or sub-category	Favours Bilevel N	Favours Control N	mean difference (SE)	mean difference (random) 95% CI	Weight %	mean difference (random) 95% CI
Ambrosino 1992	7	7	6.0000 (2.3904)		30.97	6.00 [1.31, 10.69]
Highcock 2003	8	8	-2.0000 (2.0000)		34.28	-2.00 [-5.92, 1.92]
Nava 1993	6	7	-1.0000 (1.9456)		34.75	-1.00 [-4.81, 2.81]
Total (95% CI)	21	22			100.00	0.83 [-3.77, 5.42]

Test for heterogeneity: Chi² = 7.45, df = 2 (P = 0.02), I² = 73.1%
Test for overall effect: Z = 0.35 (P = 0.72)



Respiratory Muscle Function/Work of Breathing

Figure 13
Combined Analysis for Maximal Inspiratory Pressure (MIP cm H20) on COPD RCTs

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 01 RCT Trials of Bilevel NIPPV versus all modalities (LTOT, Sham ventilation, Excercise)
Outcome: 06 MIP cm H20

Study or sub-category	N	Bilevel Mean (SD)	N	Control Mean (SD)	Weight %	WMD (random) 95% CI
Clini 2002	38	50.60(20.60)	46	48.10(27.20)	77.00	2.50 [-7.73, 12.73]
Renston 1994	9	48.00(19.50)	8	37.00(19.80)	23.00	11.00 [-7.72, 29.72]
Total (95% CI)	47		54		100.00	4.45 [-4.52, 13.43]

Test for heterogeneity: Chi² = 0.61, df = 1 (P = 0.43), I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

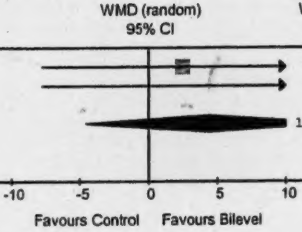


Figure 14
Combined Analysis for Maximal Inspiratory Mouth Pressure (PImax cmH20) on COPD Crossover Trials

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 10 Maximum Inspiratory Pressure (PImax cm H20)

Study or sub-category	Favours Control N	Favours Bilevel N	mean difference (SE)	Weight %	mean difference (random) 95% CI
Lien 1993	11	11	0.4000 (12.8142)	3.35	0.40 [-24.72, 25.52]
Lin 1996	10	12	5.0000 (2.3839)	96.65	5.00 [0.33, 9.67]
Total (95% CI)	21	23		100.00	4.85 [0.25, 9.44]

Test for heterogeneity: Chi² = 0.12, df = 1 (P = 0.72), I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)

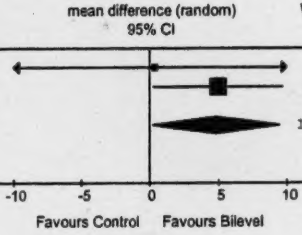
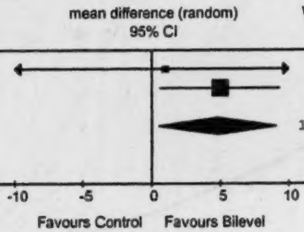


Figure 15
Combined Analysis for Maximal Expiratory Mouth Pressure (PEmax cmH20) on COPD Crossover Trials

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 11 Maximum Expiratory Pressure (PEmax cm H20)

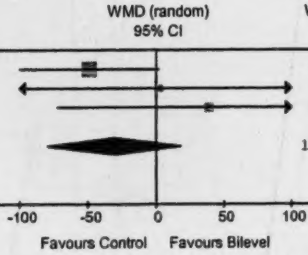


Study or sub-category	Favours Bilevel N	Favours Control N	mean difference (SE)	Weight %	mean difference (random) 95% CI
Lien 1993	11	11	1.0000 (10.3830)	4.40	1.00 [-19.35, 21.35]
Lin 1996	10	12	5.0000 (2.2265)	95.60	5.00 [0.64, 9.36]
Total (95% CI)	21	23		100.00	4.82 [0.56, 9.09]

Test for heterogeneity: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%
Test for overall effect: Z = 2.22 (P = 0.03)

Figure 16
Combined Analysis for Exercise Tolerance: 6 Minute Walk Test (meters) on COPD RCTs

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison: 01 RCT Trials of Bilevel NIPPV versus all modalities (LTOT, Sham ventilation, Excercise)
Outcome: 04 Excercise Testing - 6 min. walk test (meters)



Study or sub-category	N	Bilevel Mean (SD)	N	Control Mean (SD)	Weight %	WMD (random) 95% CI
Clini 2002	37	183.00(118.00)	42	232.00(111.00)	77.81	-49.00 [-99.72, 1.72]
Gay 1996	4	312.00(240.60)	6	309.80(111.00)	3.69	2.20 [-249.76, 254.16]
Renston 1994	9	273.00(138.00)	8	234.00(93.34)	18.49	39.00 [-71.96, 149.96]
Total (95% CI)	50		56		100.00	-30.83 [-79.44, 17.77]

Test for heterogeneity: Chi² = 2.07, df = 2 (P = 0.35), I² = 3.6%
Test for overall effect: Z = 1.24 (P = 0.21)

Figure 17
Combined Analysis for Dyspnea on COPD RCTs

Review:	A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Pulmonary Disorders
Comparison:	01 RCT Trials of Bilevel NIPPV versus all modalities (LTOT, Sham ventilation, Excercise)
Outcome:	05 Dyspnea Rating

Study or sub-category	N	Bilevel Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
Casanova 2000	20	5.00(1.63)	24	4.00(1.63)		50.12	1.00 [0.03, 1.97]
Renston 1994	9	0.70(0.90)	8	1.30(1.13)		49.88	-0.60 [-1.58, 0.38]
Total (95% CI)	29		32			100.00	0.20 [-1.37, 1.77]

Test for heterogeneity: $Chi^2 = 5.19$, $df = 1$ ($P = 0.02$), $I^2 = 80.7\%$

Test for overall effect: $Z = 0.25$ ($P = 0.80$)